

AN ESSAY
ON THE PATHOLOGY AND TREATMENT
OF
MÉNIÈRE'S DISEASE

submitted by
M. Spencer Harrison, M.D. Edin.



INTRODUCTION

In an essay on a condition named after Ménière it may be considered appropriate to discuss the accenting of his, one of the best known names in the literature of otology.

Even during his lifetime there appears to have been no uniformity in the accenting of Prosper Menière's name. Thus, though his original publications are signed 'Menière', yet, following a paper read before the Academy of Medicine he is described in the official report as Dr. 'Ménière'. This style is also to be found in the unofficial report in the Gazette Médicale de Paris, and Trousseau, who addressed the same Academy one week later, also referred in his report to Dr. Ménière. Ménière is the form which appears on his tombstone and this is also used by his son Paul, the otologist.

In the German literature both styles commonly occur. Thus 'Menière' is used by Schwartz, Politzer, Bárány and Nager; Ménière, with two accents, by Jacobson, Steurer and Volkmann-

Hoffmann. In the English medical literature one finds only Ménière and this form is also usual in the French works (Laurens, Larousse and the Catalogue of the Bibliothèque Nationale) and also in some contributions by French authors to German textbooks (Chauveau and Montandon).

In Dauzat's etymological dictionary of French family names the name is spelt Ménier with the variants Maynier, Meynier, Mesnier and Mener. The author catalogue of the French National Library, too, often contains the name, usually as Menier or Ménier, the latter form being more common in later years, and the style Menière may have developed from Menier in this way. Although the style Menière was always used by the author himself in attaching his signature to letters and papers, it seems equally clear that the form Ménière has been more generally used by others and must now be considered acceptable.

Although the triad of symptoms of vertigo, tinnitus and deafness is a fairly common affliction and had been known for a century before his time, it was not until 1861 that Ménière

published his well-known description. The case was that of a young girl, who, after exposure to cold, was attacked by sudden deafness, intense vertigo, vomiting and pyrexia, followed by death in five days. Post-mortem examination revealed a reddish-yellow coagulum within the labyrinth, and it has since been customary to regard the case as an instance of acute haemorrhagic labyrinthitis or of leukaemic involvement of the internal ear similar in type to two cases seen in the author's experience in recent years. Both cases developed acute labyrinthine symptoms in the late stages of leukaemia. In both cases admission to hospital was because of an attack of acute prostrating vertigo, though progressive lassitude had been present for some months. The contents of the labyrinth were macroscopically very similar to those in this case described by Ménière. It is interesting that in both cases the leukaemic cells ^were mainly in the perilymph spaces. The clinical findings in one of the cases follows:-

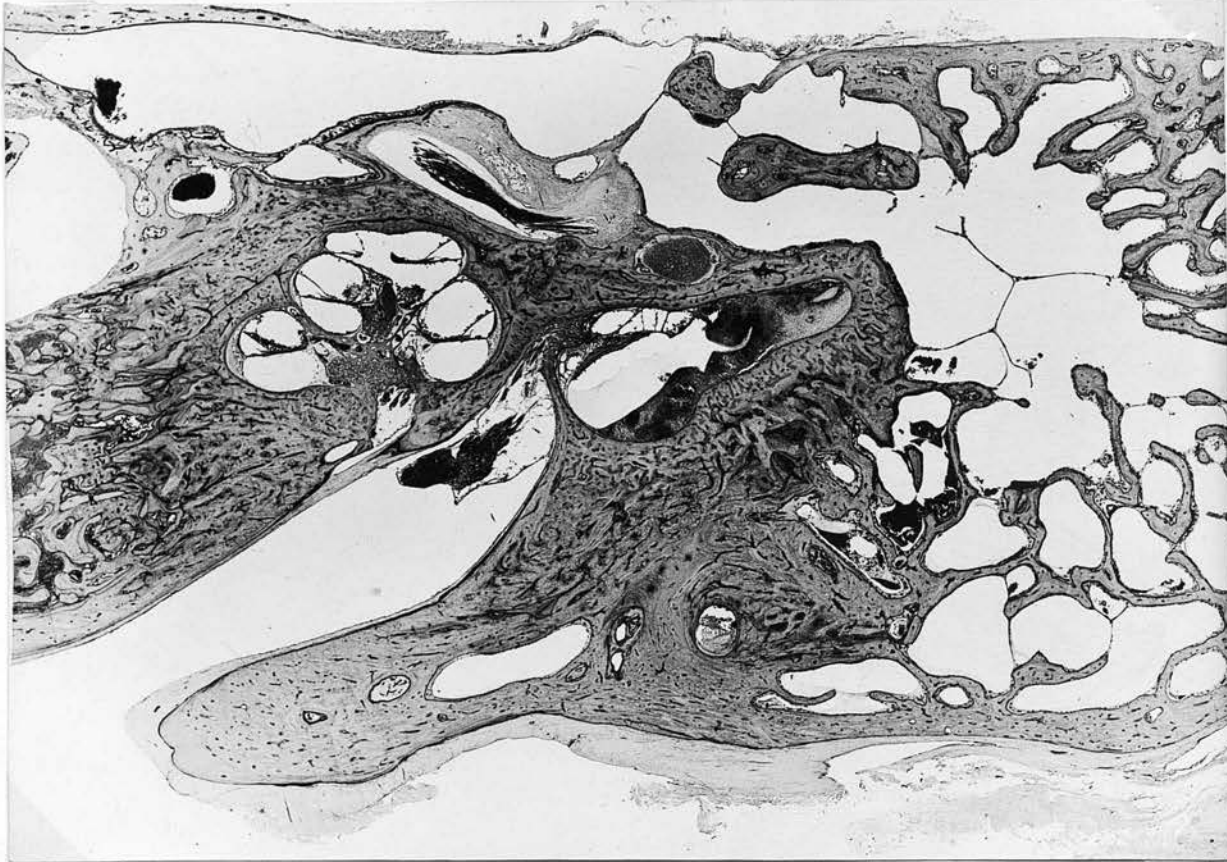


Fig. 1. Low power view right temporal bone (O. 4.3x)



Fig. 2. Macula utriculi and ampulla of external canal. (O. 12.4 x)

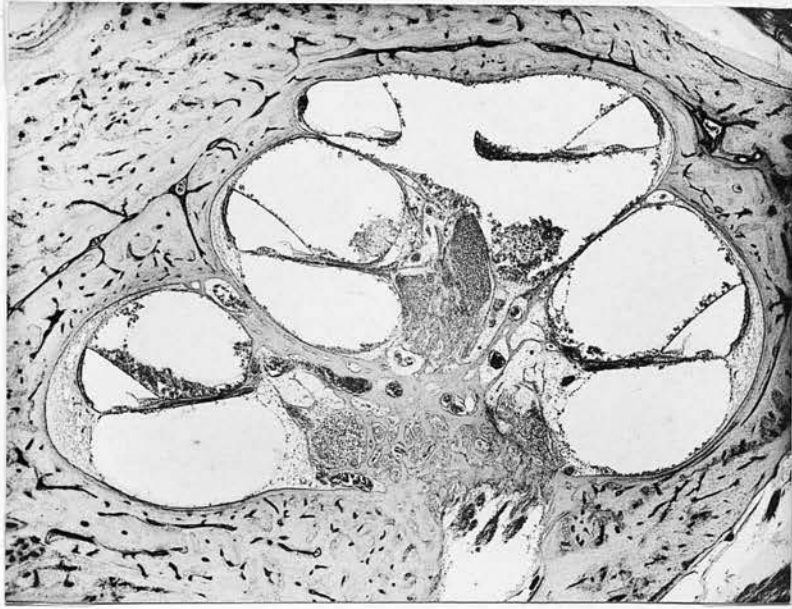


Fig. 3. Cochlea (O. 10.9 x)

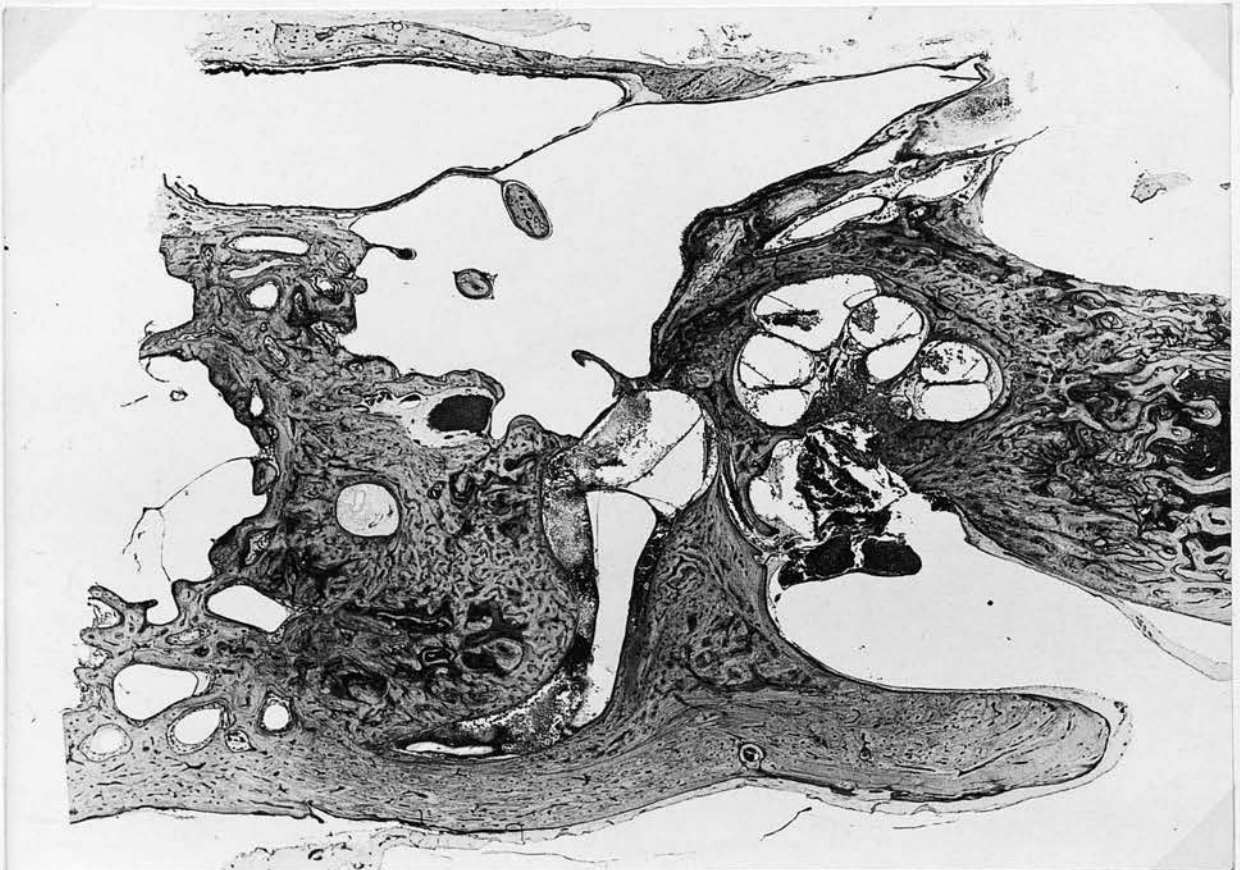


Fig. 4. Low-power view, left temporal bone. (O. 4.3 x)

The patient, a married woman of 43 years, was admitted to hospital on August 19th 1946, complaining of progressive lassitude for eight months. One week before admission the patient noticed that her vision had become misty. Later the same day she suddenly became dizzy and "seemed to be spinning round". This vertigo was relieved by lying down but recurred if she sat up or moved. Vomiting occurred mainly after meals and four days later tinnitus developed. This she described as "a noise like a threshing machine going on all the time".

On examination, marked enlargement of the spleen was present and vestibular nystagmus was present both to the right and to the left, being more marked to the right. Hearing tests carried out with a watch only showed slight bilateral impairment. The tympanic membranes were normal and no other abnormalities of the central nervous system were found. Blood examination on August 28th showed a red cell count of $2\frac{1}{2}$ millions per c.mm. White cell count 760,000 per c.mm. Most of the white cells seen were myelocytes. The patient died suddenly from a cerebral

haemorrhage on August 29th. The temporal bones were removed ten hours after death, fixed in formalin and embedded in the usual way in celloidin.

It is much to be regretted that for clinical reasons a more complete otological examination was impossible. The patient was severely ill at the time of her examination and no detailed tests of cochlear or vestibular function could, therefore, be carried out and, in point of fact, little more was possible than to recognize the severe character of the vestibular derangement. Furthermore, that cochlear function was relatively little impaired. As to the pathological changes, they show in the first place a remarkable symmetry in the two labyrinths, with a marked predilection for the sub-epithelial tissues in the region of the macula utriculi and the ampulla of the horizontal canal. It seems likely that the leukaemic cells scattered about the scala vestibuli of the cochlea have found their way there from some haemorrhagic focus in the perilymph spaces of the vestibule.

The cochlea, apart from these scattered leukaemic cells,

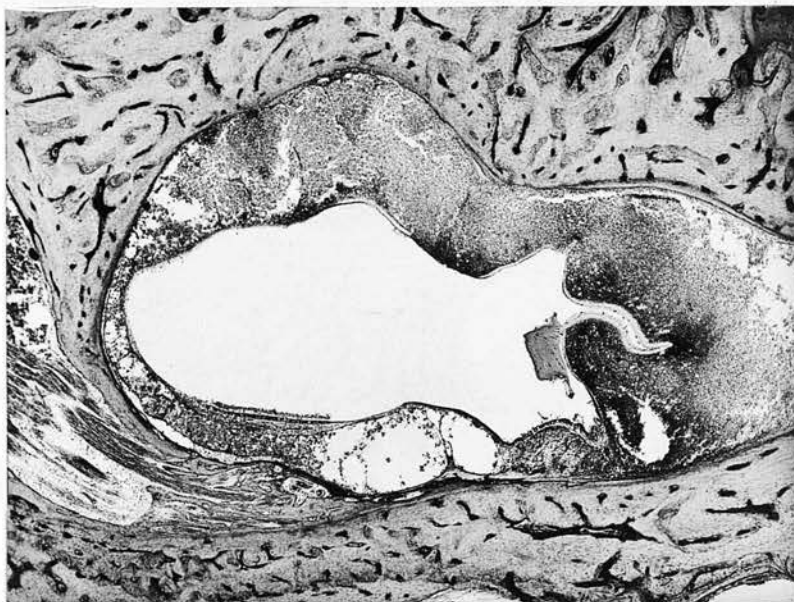


Fig. 5. Macula of utricle and ampulla of horizontal semi-circular canal. (O. 12.4 x)

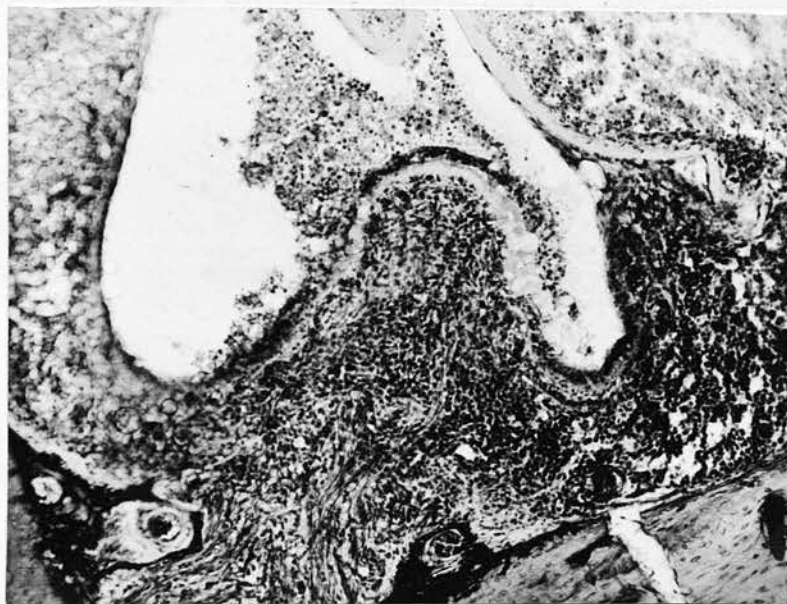


Fig. 6. Ampulla. (O. 75 x)

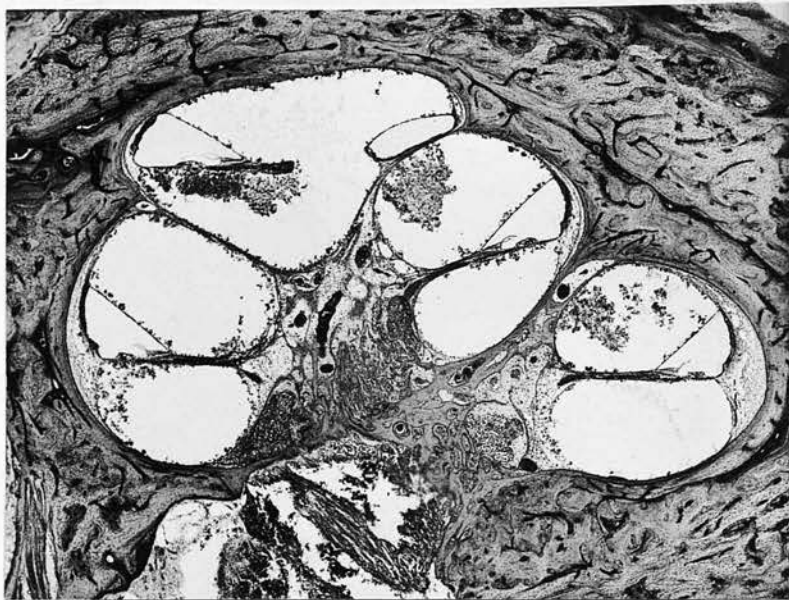


Fig. 7. Cochlea (O. 10.9 x)

appears relatively well preserved, and this seems to accord well with the evidence, unsatisfactory as it is, of fairly good cochlear function.

As regards the leukaemic cells themselves, a point of importance was the presence in most areas of red cells, for the most part well preserved, in numbers which correspond to their proportions in the blood stream, a fact which establishes their recent haemorrhagic origin.

Since his original papers appeared Ménière's name has come to be attached somewhat loosely to a variety of clinical conditions presenting the syndrome of vertigo, tinnitus and deafness. In some of these, signs and symptoms of cochlear and vestibular upset are clearly recognizable as being due to inflammatory, neoplastic or other processes involving the labyrinth, the eighth nerve, or its central connections. With these excluded, however, there still remains a considerable group in which these signs and symptoms present certain recognizable peculiarities in their mode of onset, character and clinical

course. The papers of Crowe (1938) and of Wright (1937) did much to clarify our views on the clinical identification of this group of subjects. Both of these authors were agreed in attributing the condition to a specific variety of labyrinthine disease, and their views were strongly supported by the publication in 1938 and subsequently by Hallpike in association with Cairns, -1 Wright (1940) and Harrison (1954) of the histological findings in the temporal bones of four cases of this kind. In all, the affected labyrinth was found to be the seat of certain peculiar changes indicative of an obstructive distention of the endolymph system. These findings have since been confirmed by several other authors and it is now possible to regard these investigations as having established the morphological basis of a disease sui generis of the labyrinth.

According to modern views based upon these clinical and pathological studies, the term 'Ménière's disease' should be reserved for this particular group of cases readily recognizable

Figs. 8, 9 and 10, from the second case of leukaemia of the labyrinth show similar appearances to the above.

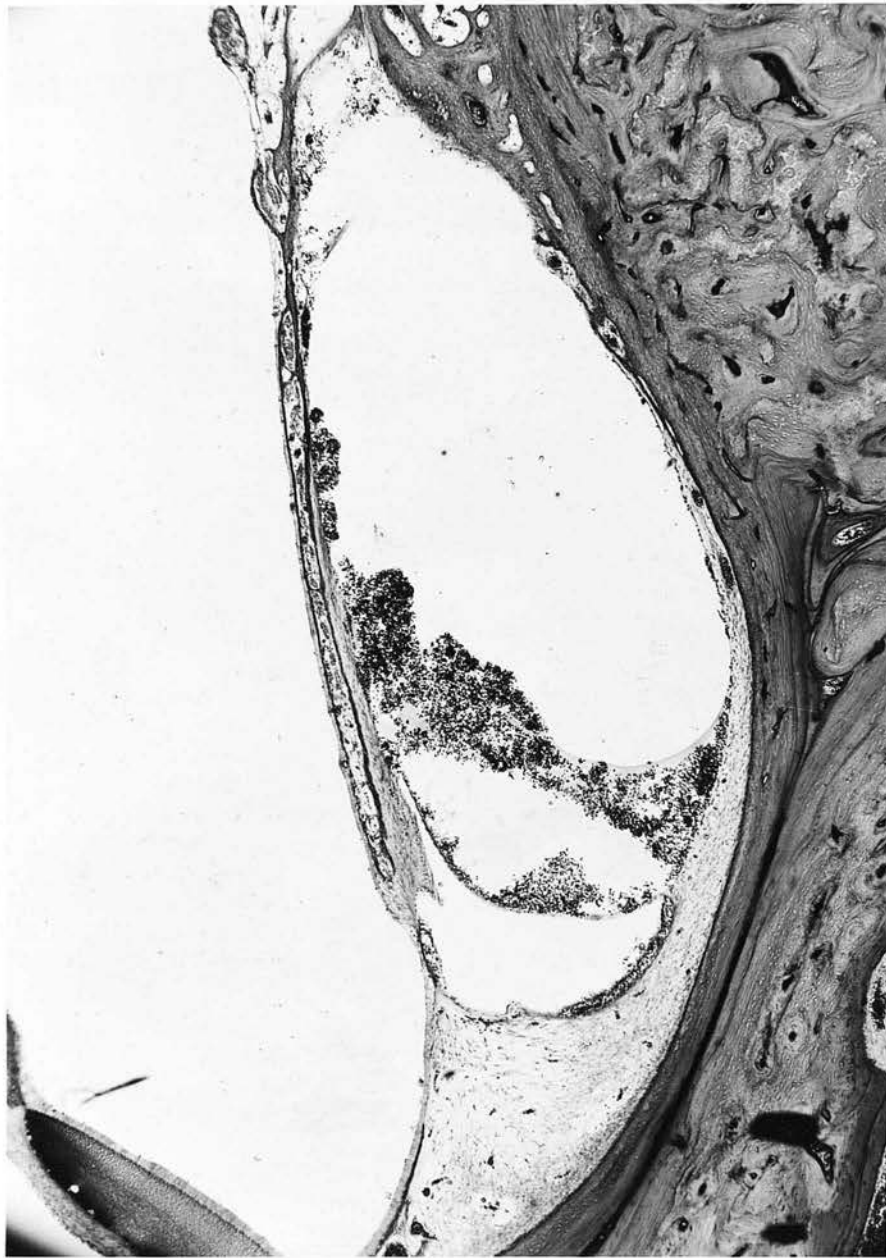


Fig. 8. Cochlear shows cells in the perilymph spaces but not in the endolymph.



Fig. 9. Perilymph spaces of canal and utricle show similar appearance.

as a clinical entity and presenting within the labyrinth the specific type of morbid change indicative of endolymphatic distention.

AETIOLOGY AND PATHOLOGY

Until recently, what was known of the pathology of the disease had been learnt from the many empiric attempts at treatment, but arising out of the clinical, pathological and biochemical methods of investigation, conducted quite independently, the fact has emerged that a large number of these cases are suffering from one clinical entity. The disease is a chronic and progressive condition affecting the labyrinth and reports of the histological appearances of this organ taken from cases coming to post-mortem, are now available to prove the contentions of the clinical observers.

Clinical

Clinical data have been collected by a number of observers showing that in a large proportion of patients the signs and symptoms of cochlear and vestibular disorder present certain

peculiarities in their mode of onset, in their type and degree, and also in the course which they pursue over a period of years, there is thus agreement/ⁱⁿattributing them to some specific type of labyrinthine disorder. From observations on patients before and after the division of the eighth nerve Crowe (1938) came to the conclusion that the attacks were due to abnormalities in the normal pressure and the biochemistry of the endolymph. He postulated an excitation, a hyperfunction of the labyrinth, though later work suggests the condition is more of the nature of a hypofunction. Both Crowe and Wright (1937), however, were convinced that the symptoms were produced by a specific and common cause, though the latter arrived at the conclusion by a different method. Wright studied approximately a hundred cases and found septic foci in a large proportion of them; in fact 33 per cent of his cases showed more than one focus, the commonest sites being in the tonsils, teeth, sinuses, gall-bladder and uterus. As it was not always possible to get rid of such an infection, however, a failure to achieve a cure as a



Fig. 10. Illustrates the intact endolymph space.

result of treatment in an individual case might not necessarily prove that the conception was wrong. He believed that a bacterial intoxication of the labyrinth which he called 'focal labyrinthitis' results. Cawthorne et al. (1942) in fifty cases of Ménière's disease found definite evidence of sepsis in only a small number, and even these were not all benefited by the eradication of the focus. Other otologists (Shambaugh, 1940) have not observed a high proportion of sepsis occurring in these cases yet they recognize that this type of case does exist and to this extent they confirm the validity of Wright's hypothesis.

With the almost universal cure of the vertigo, although not always of the tinnitus, in a large number of cases by the division of the eighth nerve or its vestibular portion the origin of the symptoms may be placed in Scarpa's ganglion or in the labyrinth. Impressed by the clinical resemblance to glaucoma, Cheatle suggested many years ago that decreasing the intra-labyrinthine pressure might cure the symptoms. The accuracy of this deduction was proved by Lake (1904) and since

then many clinicians have cured the vertigo by destruction of the labyrinth (Mollison, 1935 a; Wright, 1942). These observations located exactly the seat of the disease and showed that the intra-labyrinthine tension and possibly also the biochemistry of the endolymph, are important factors.

Pathological

Since the classical papers of Hallpike on the histology of Ménière's disease it has gradually been accepted that this disease is a disorder peculiar to the human labyrinth in which hydrops of the labyrinth (or hydrolabyrinth) chiefly of the cochlear portion and the saccule occurs associated with degenerative changes of the sensory cells, in particular the hair cells of Corti's organ. The appearances of the labyrinth show some variation and comparison is rendered difficult by the planes of section failing to correspond, some being horizontal and some vertical. All the cases show dilatation of the whole endolymph system, and in some cases it has been gross. Expansion of the scala media stretches Reissner's membrane and may push it

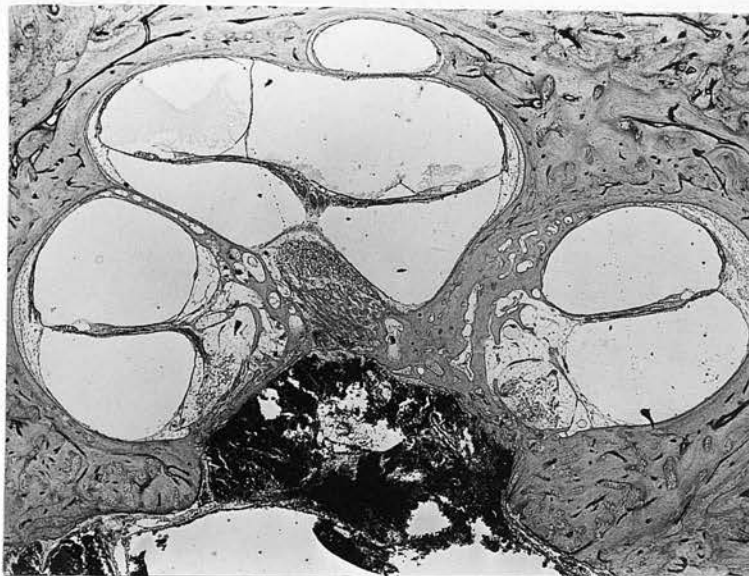


Fig. 11. Left temporal bone. The cochlear. Showing the maximal dilatation of the scala media. In the anterior basal whorl the displacement of Reissner's membrane is not complete. The membrane is fixed by newly formed connective tissue.



Fig. 12. The cochlea showing gross dilatation of the scala media with displacement of Reissner's membrane onto the wall of the scala vestibuli. At the apex, Reissner's membrane has been displaced through the helicotrema into the scala tympani.

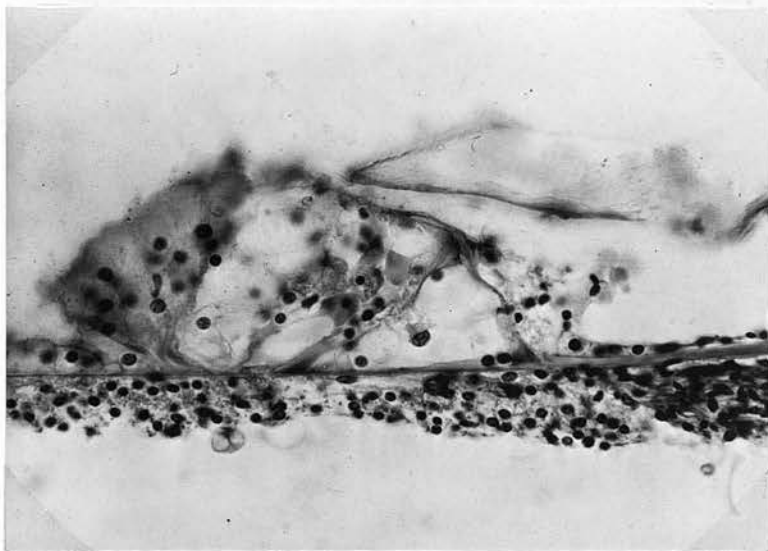


Fig. 13. Organ of Corti (human) showing the appearance of a fairly advanced degree of post-mortem degeneration.

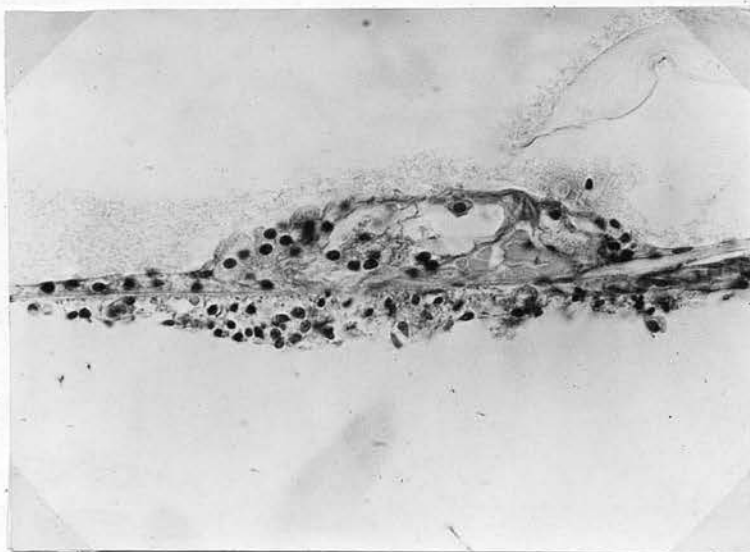


Fig. 14. Left temporal bone. Corti's organ, showing degenerative changes.

outwards against the walls of the cochlea, to which in many cases it has become adherent so obliterating the scala vestibuli, and bulging through the helicotrema. The organ of Corti has shown degeneration in late cases in which post mortem changes have not invalidated the result. The cells of the organ of Corti are notoriously difficult to display in histological preparations of the human temporal bone. Nevertheless it is possible to detect certain obvious pathological changes as in fig.13 . Above is shown the organ of Corti of the unaffected ear with its hair cells and Corti's rods enclosing a well-formed tunnel. Below, ^(fig.14) on the affected side, the cell mass of Corti's organ is greatly compressed and its outline irregular, while Corti's tunnel is occupied by a structureless coagulum. The number of hair cells in Corti's organ could not be determined in most of the cases because of the post-mortem changes. Dix and Hallpike (1952) have found evidence of degeneration of the hair cells in one case. Schuknecht (1953) was able to show no significant difference in the hair cell count between normal

and affected sides. In early cases clinical experience would suggest little change in the hair cell count as the hearing returns to normal from a threshold depressed as much as forty decibels. At times the basal turn of the cochlea shows degenerative changes of Corti's organ to a greater degree than the remainder. These findings are similar to those found in senile deafness and certain forms of degenerative or toxic types of deafness, but in some cases the possibility of co-existing old-age deafness must be considered.

Degenerative changes have also been noted in the sensory epithelium of the vestibule, but the stria vascularis (according to Guild, 1927, the site of formation of the endolymph) is relatively unharmed histologically and perhaps still less so functionally since its blood supply is arranged so that it is protected against a rise of pressure in the duct (Belemer 1936). The vessels pass through the modiolus across the roof of the scala vestibuli and enter the stria at its upper border. Thereafter they pursue a course of varying obliquity through

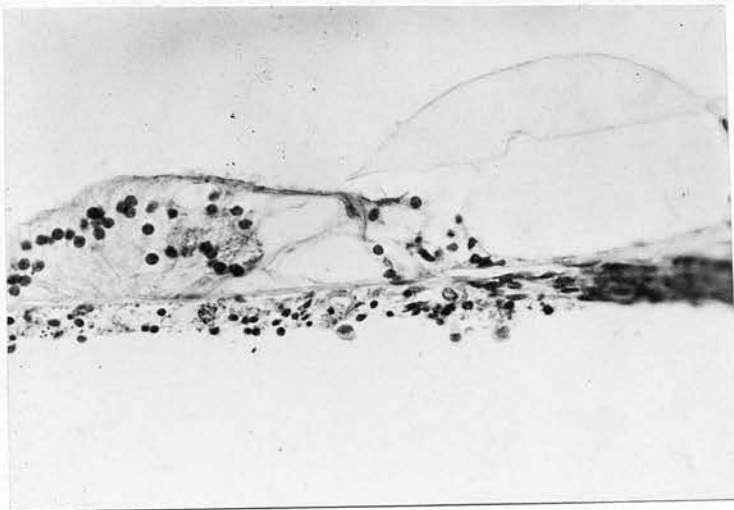


Fig. 15. Right temporal bone. Corti's organ showing a moderate degree of post-mortem degeneration. No pathological change is recognizable.



Fig. 16. The saccus endolymphaticus showing the 'normal' area of soft connective tissue surrounding the saccus.

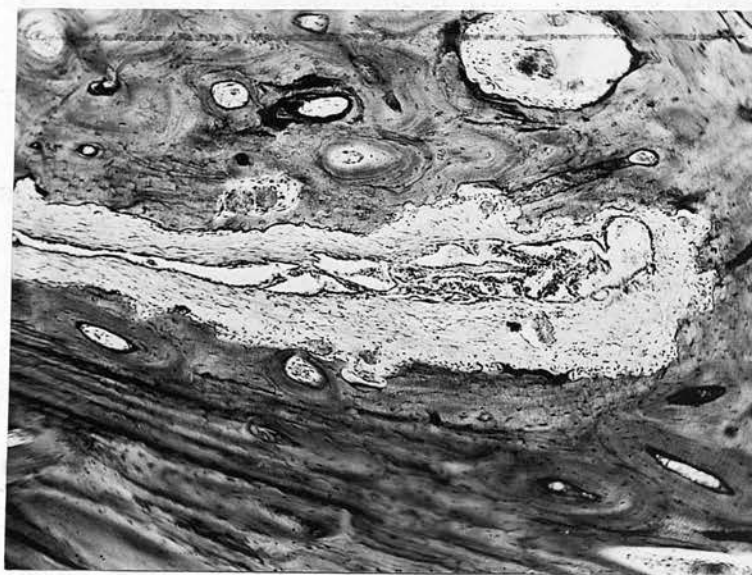


Fig. 17. Saccus endolymphaticus from a patient without a known history of deafness. There is an atypical absence of the area of soft connective tissue around the saccus.

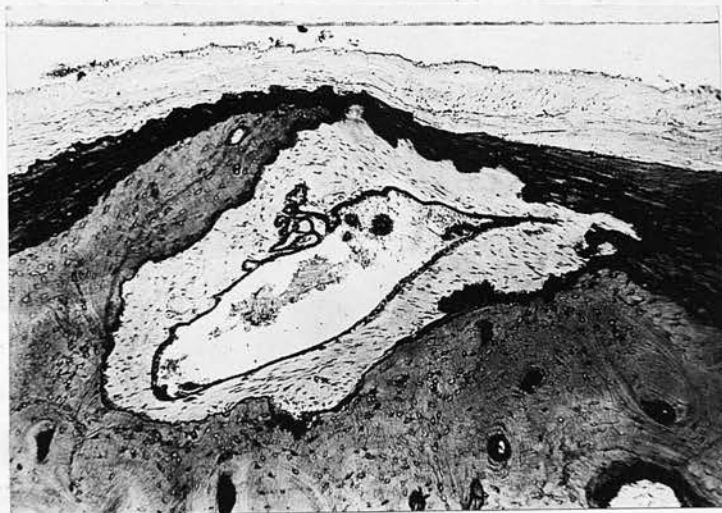


Fig. 18. Right temporal bone, showing the absence of the normal perisaccular connective tissue.

the stria, to emerge once more from its lower border into the substance of the spiral ligament. Belemer emphasises the remarkable character of an anatomical arrangement whereby arterioles entering a capillary field so small and well defined as the stria vascularis should leave it with their form substantially unchanged. He considers that the arterioles, by variation in their calibre, may influence the tension of the basilar membrane, and supports the suggestion by the observation of a particular relationship of the emerging arterioles to the oblique fibres of the spiral ligament. The important finding is the numerous arterioles within the stria, the maintenance of their calibre in their passage through the stria, and their intimate relationship to its superficial cells.

It appears then that the capillary supply from the arterioles to the secretory elements is delivered at a particularly short range and consequently at such a pressure as to enable the stria to continue to maintain its function under conditions of increased pressure in the surrounding fluids.

Dilatation of the saccule is fairly constant and in some cases the ductus reuniens and the saccular duct have been dilated so that the saccule may be herniated into the small end of the horizontal canal. Localised dilatations or bulgings probably indicate the presence of weak or unsupported points in the walls of the utricle.

Little change in the peripheral cochlear neurone has been shown. The ganglion cells are present in the same density in the affected as in the normal ear.

Brunner (1948) states that it has long been known that hydrolabyrinth may be discovered in patients who have suffered from spells of vertigo, that it may occur secondary to a serous labyrinthitis, is frequently to be seen in Schieb's type of congenital deafness, also as a result of cholesteatoma of the mastoid, tuberculous otitis and other conditions. While no decisive objection can be made to this interpretation, it is necessary to emphasise that such extreme and uniform dilatation of the endolymph system is very rarely seen in serous labyrinthitis.



Fig. 19. Saccus endolymphaticus showing the absence of the normal perisaccular connective tissue.

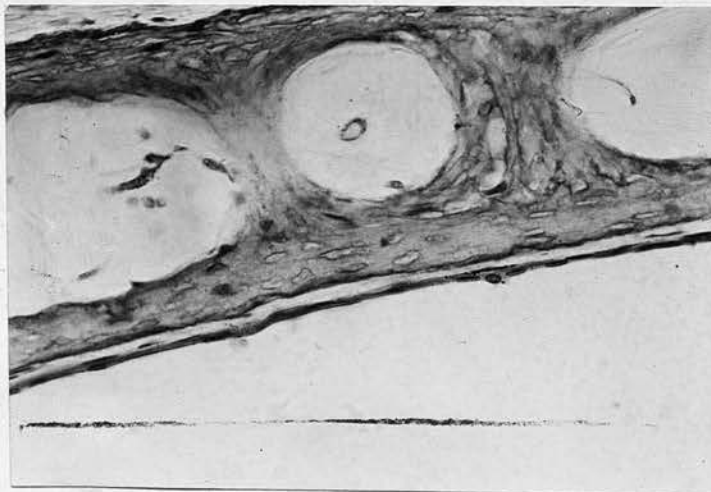


Fig. 20. Left temporal bone. Showing a view of the scala vestibuli. Reissner's membrane can be seen flattened against its bony wall.

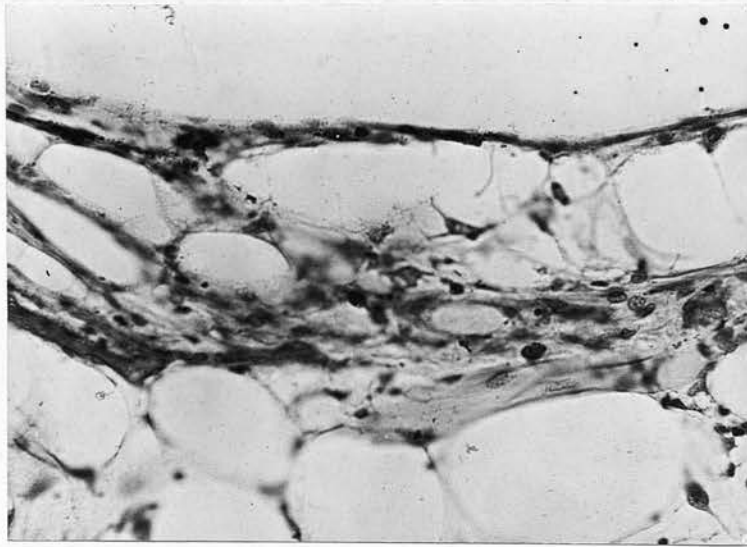


Fig. 21. Left temporal bone. Fixation of Reissner's membrane (left) by organising connective tissue elements.



Fig. 22. Lateral semicircular canal showing sub-epithelial vesiculation and albuminoid coagulum in the perilymph space.

and also that while the histological changes in Corti's organ from cases of Ménière's disease may represent some undescribed stage of serous labyrinthitis, they do not present those features described by Witmaack (1929) and others as being most typical of this condition. On the other hand it is still necessary to admit the possibility that the distension might, in fact, be a reaction to haemorrhage or infection, and further, that the distension might persist and dominate the histological picture long after all evidence of the primary factor, be it haemorrhage or infection, has disappeared.

A decision between these two points of view is of more than academic interest. Indeed, upon it must depend the design and in all probability the success of the further lines of enquiry which will be needed before we understand the nature of this troublesome disorder and are able to control its manifestations with intelligence.

The histological findings in the patient with leukaemia described above give us some help in making this decision. As

judged by our patient's symptoms, the labyrinthine lesions appear to have had their onset within a comparatively short period - 17 days before death. With this the detailed histological character of the leukaemic deposits in the labyrinths is in good agreement. If, therefore, endolymphatic distension were a non-specific type of reaction of the inner ear to infection or haemorrhage, then we might have expected its occurrence in this case. Nevertheless, no trace of a distension reaction on the part of the endolymph system can anywhere be detected.

This, we think, lends support to the arguments of Cairns and Hallpike that the endolymphatic distension so characteristic of Ménière's disease is due to a specific disorder of the endolymph circulation. What still remains obscure is the mechanism of this distension. Serous labyrinthitis is usually a reversible condition and it appears that the distension must have been of considerable degree and duration before an irreversible effect on Corti's organ results.

Brunner agrees that distension of the endolymph system occurs in Ménière's disease, though not in all cases, but as Williams (1952) suggests, Brunner's criteria for diagnosis are not the same as those of most present day otologists. Also in the early stages of the disease the increase in tension of the endolymph may not be permanent and the membranes still sufficiently elastic to return to their original position before the changes in fluid content occur. Hence Brunner's statement that the hydrolabyrinth may not be a prerequisite but rather an eventual result of Ménière's disease. On the other hand many otologists believe that vertigo or dizziness do not occur in every case of Ménière's disease and that the finding (Lindsay 1942) of distension of the endolymph system in a case of end-organ deafness may thus be explained, or it may be as Lindsay postulates, the dizzy spells may have occurred long before the patient was seen and the condition diagnosed as labyrinthine deafness. Ménière's disease is probably a much more common cause of progressive perceptive deafness than is generally

realised (Dix and Harrison, 1948).

The finding of relatively normal conditions in the utricle and canal, coincident with destruction of the cochlear part of the endolymphatic system, is difficult to explain and has been held to suggest (Seymour 1954) that the fluid system of this part of the membranous labyrinth can be maintained from some other source such as the saccus endolymphaticus. In this connection Seymour finds an interesting functional application for an anatomical feature of the membranous labyrinth to which attention was first directed by Bast (1928), the utriculo-endolymphatic valve. According to Seymour, this valve allows fluid to flow from the saccus endolymphaticus into the utricle, but prevents its return. Seymour's histological observations upon the saccus itself also led him to conclude that it has an important secretory function. Its fluid contents, formed in situ, would thus be able to pass into the utricle and semicircular canals and maintain their function without reference to the cochleo-saccular portion of the membranous labyrinth.

But the excellent microscopic studies of Secretan (1944) led him to conclude that the histological features of the saccus which Seymour describes should rather be interpreted as evidence of its absorptive function. Secretan examined the anatomy of the utriculo-endolymphatic valve and found there was good reason for doubting Bast's interpretation of its function. Secretan, whilst not denying the existence of the valve as described by Bast, shows that there may be considerable individual variations in its structure. He shows also that there is another fold in this region, (fig. 23&4) the utriculo-saccular fold (this appears in Bast's photomicrographs but is not mentioned in the text), of very much lighter structure than the formation described by Bast, and is for this reason much more likely to act as a mobile valvular element.

If this explanation is accepted, and Secretan's argument appears very well founded, there would be no anatomical basis for a one-way movement of fluid from the saccus to the utricle, as Seymour suggests. Hallpike (1938) discusses the problem of

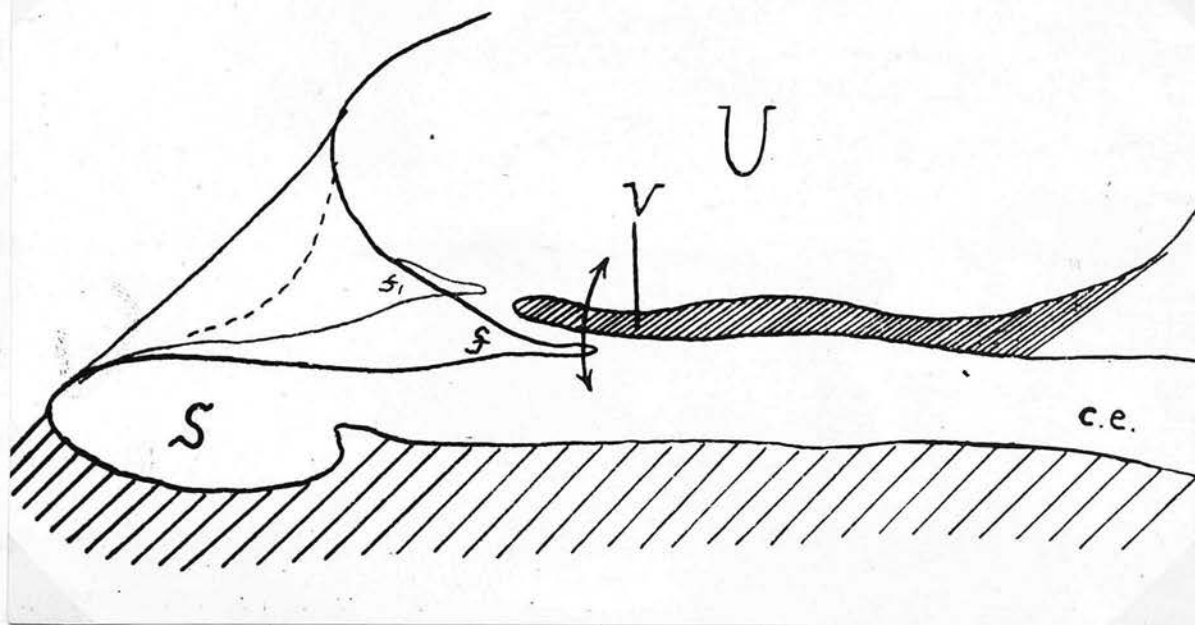


Fig. 23. Utriculo-endolymphatic valve.

V = valve of Bast.

S = saccule.

U = utricle.

c.e. = endolymphatic canal.

f = utriculo-saccular fold. It may move up to S.

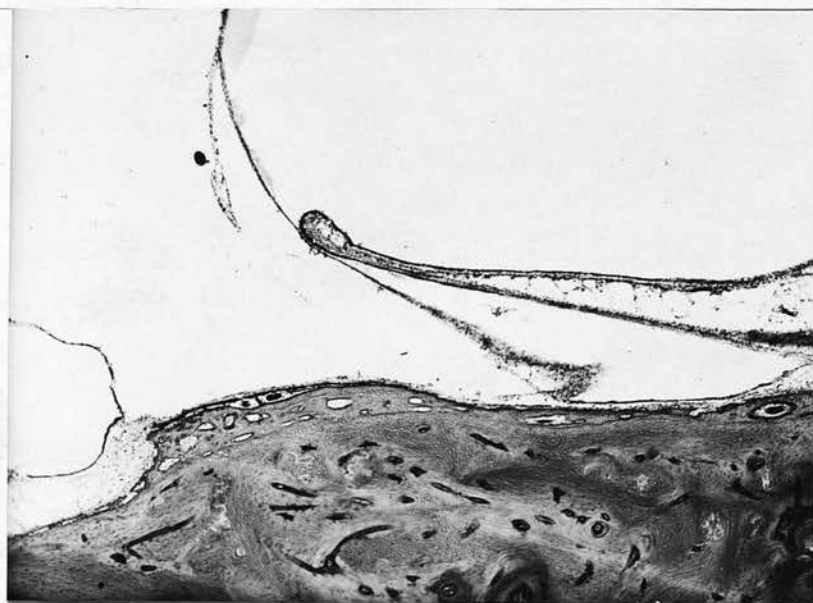


Fig. 24. Endolymphatic valve (x 35).



Fig. 25. Organ of Corti of the unaffected ear with its hair cells and Corti's rods enclosing a well-formed tunnel.

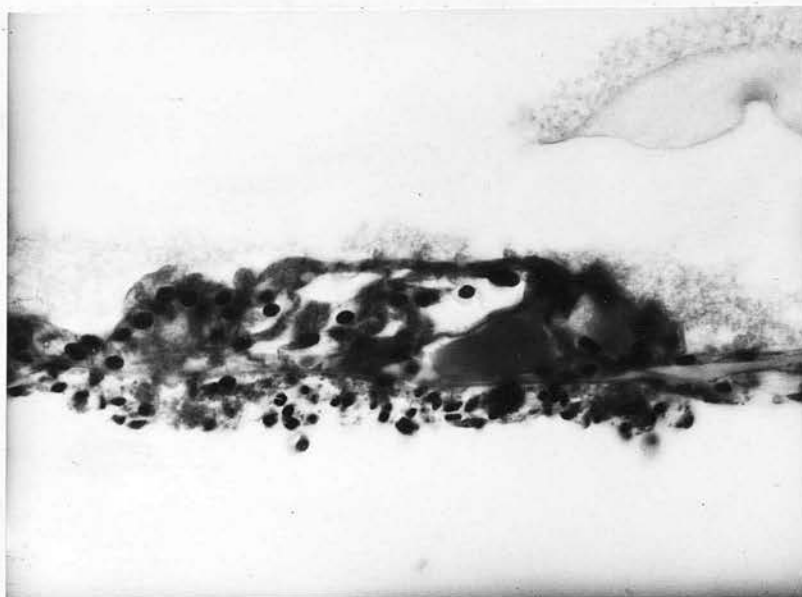


Fig. 26. Affected ear. The cell mass of Corti's organ is greatly compressed and its outline irregular, while Corti's tunnel is occupied by a structureless coagulum.

the different appearances of cochlea and sacculle - utricle and canals from the point of view of the rigidity of the utricular wall. The utricular wall appears to have an average thickness of two or three times that of the sacculle. Lempert (1952) considers that thinner portions of the utricular wall exist which would give way under pressure to produce localised distension.

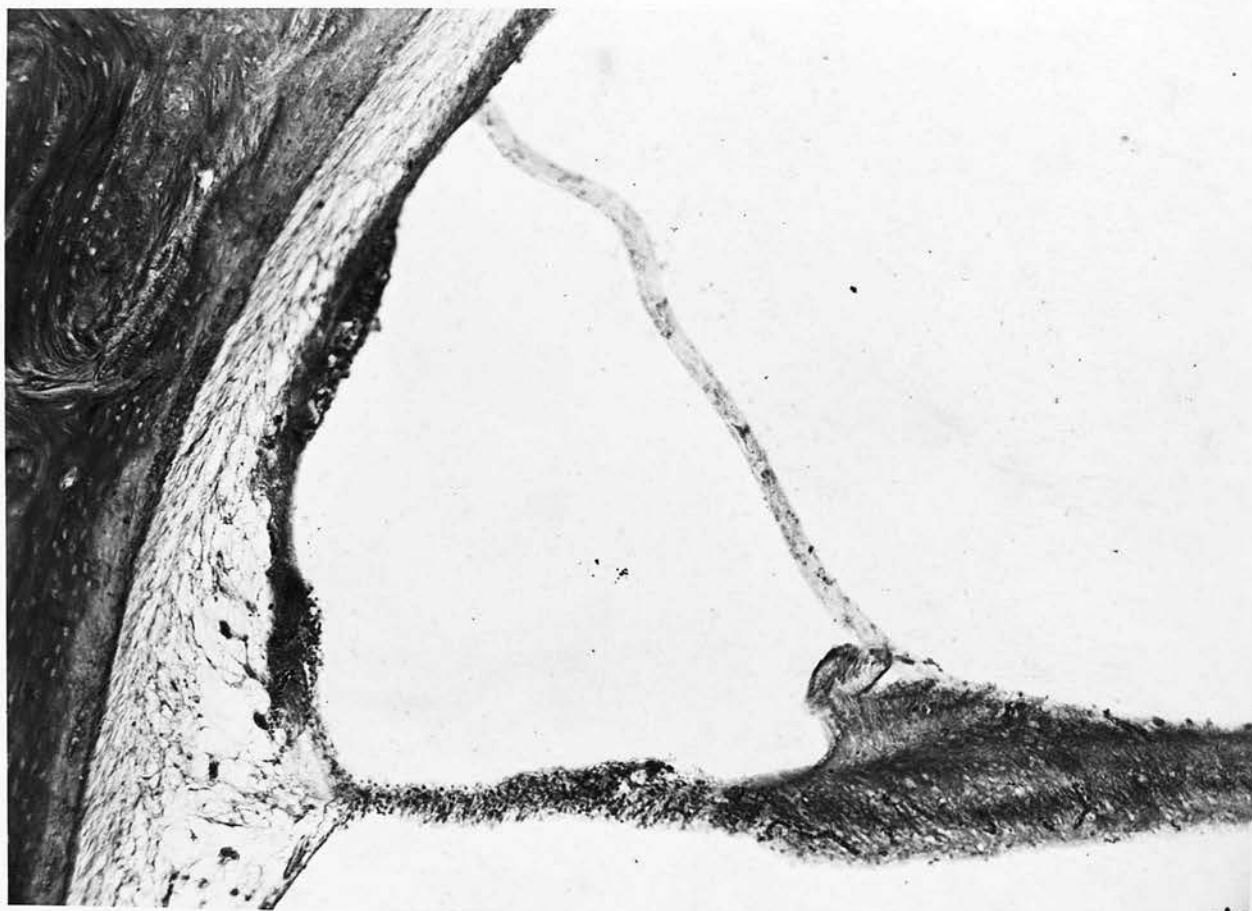
In 1927 Guild published details of experiments in which he injected a mixture of potassium, ferrocyanide and iron-ammonium citrate into the basal turn of the cochlear duct in guinea pigs and demonstrated the blue granules in the walls of the endolymphatic sac, which led him to conclude that endolymph passes towards the basal end of the cochlear duct through the ductus reuniens into the sacculle and then to the endolymphatic duct and sac. Anson and Bast (1932, 1933, 1934, 1936, 1936, 1947, 1950) have demonstrated the complex arrangement of the walls of the duct and have supported the view that this area has a resorptive function. The rugose walls, the cuboidal

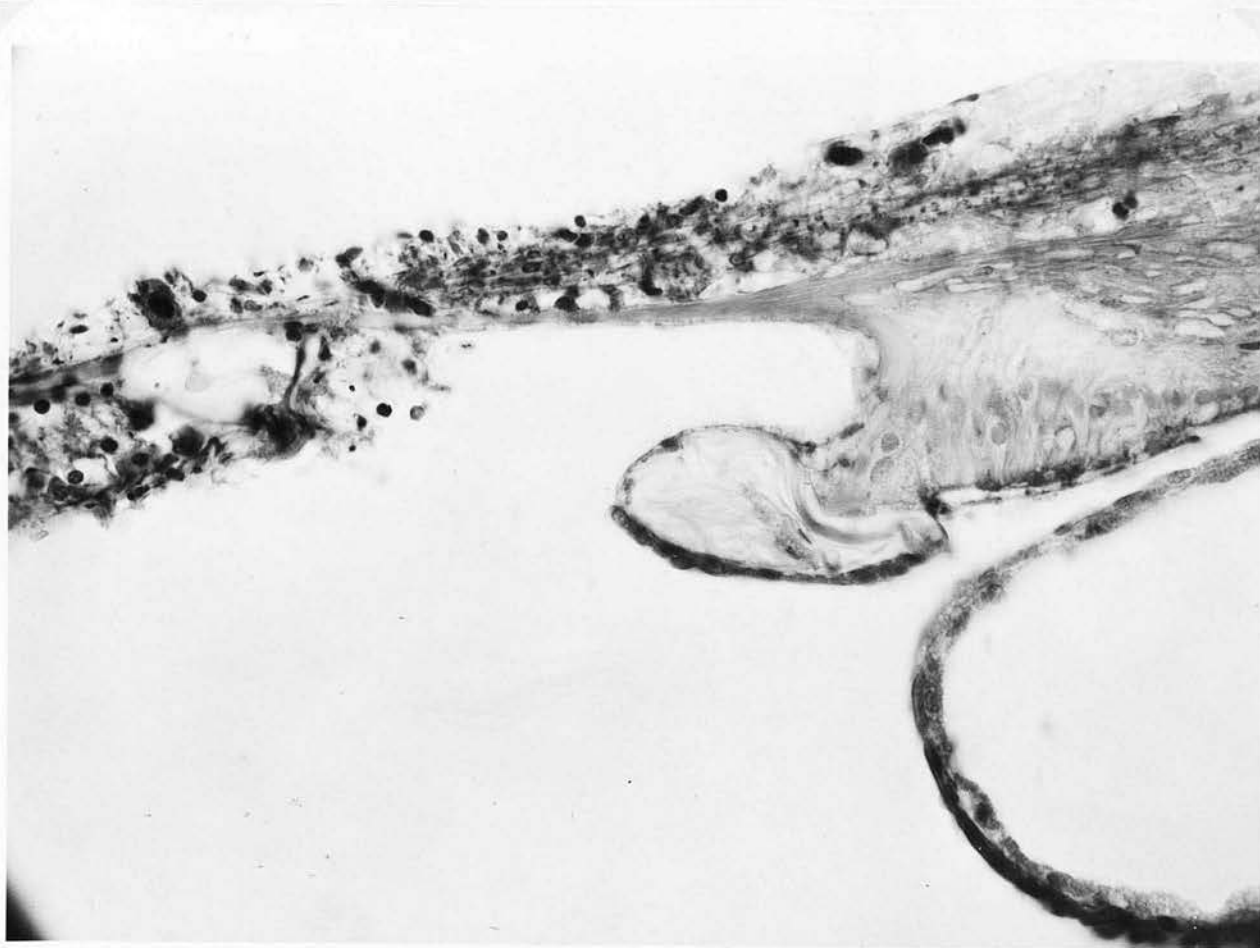
epithelium and the surrounding vascular connective tissue might well be specially designed for this purpose. Anderson (1948) and others have found experimentally there appears to be a circulation of endolymph towards the endolymphatic sac. Witmaack (1939) considered that endolymph is formed in the macula and cristae of the utricle and semicircular canals as well as in the stria vascularis.

In 1940 Hallpike postulated, on the basis of certain measurements of the pressures of the labyrinthine fluids, that the osmotic pressure of the endolymph at its source is high and that a correspondingly high osmotic perilymph pressure may be maintained by diffusion through the thin membrane separating the two fluids. He believes that endolymph is transferred actively by the excretory function of the epithelium of the pars intermedia of the endolymphatic sac into the perisaccular tissue which is at the same time distended by water attracted by the osmotically stronger endolymph. This has a dual effect: first of increasing the perisaccular pressure by the swelling of

the perisaccular connective tissue, thus opposing the further excretion of endolymph from the saccus by equalizing the pressures inside and out, and also of so reducing the osmotic pressure of the excreted endolymph as to render possible its absorption into the blood stream. This is followed by a further phase of endolymph excretion from the saccus. This hypothetical mechanism of transfer of the endolymph from the lumen of the saccus to the blood stream is supported to a limited extent by the wide variations in the bulk and consistency of the perisaccular connective tissue which are found in normal material and accounts for the apparent absence of perisaccular connective tissue in certain otherwise normal temporal bones. Hallpike (1938) and Lindsay (1956) suggested that a disturbance of the secretory apparatus might allow non-diffusible molecules to enter the endolymph. An elevation of osmotic pressure might follow with a resulting attraction of fluid through the membranes and the dilatation.

McNally (1926) showed in the rabbit no notable labyrinthine





disturbance resulted from incision, cauterisation or application of continuous pressure to the saccus endolymphaticus. Lindsay (1947 and 1952) demonstrated that destruction of the endolymphatic sac and the more differentiated medial part of the duct in monkeys and cats produced no histological change in the membranous labyrinth up to $3\frac{1}{2}$ months later, indicating that if these structures have a function it can be assumed by other structures in their absence.

Once dilatation of the endolymphatic system has attained its maximal degree the fluid system from being insensitive becomes at once extremely sensitive in its response to a given volume increase and relatively small volume increases of the endolymph give extremely rapid rises in fluid pressure.

Hallpike (1938) considered that it was possible to explain the attacks as rapidly initiated bouts of asphyxia of the labyrinthine end-organs brought about by these fluid pressure changes, the constantly increased pressure producing a chronic condition of lowered function of the affected labyrinth. The secretory

pressure of the endolymph might attain a level curtailing the supply of nutrition to the labyrinthine end-organs which is compatible with high pressure levels known to be attainable by other secretions, notably the saliva. Corti's organ derives its oxygen and other requirements through the medium of the endolymph as no capillaries are present in this organ (Kolmer 1927) and thus an increase in pressure would be unlikely to affect its nourishment. Lindsay (1956) postulated that temporary fluctuations in auditory threshold, recruitment, and hypersensitivity to loud sounds might be explained as a toxic or metabolic disturbance affecting the hair cells. Changes of this type would not be detectable by modern histological techniques. The dizzy spells he considered less predictable in their occurrence and / ^{with} no definite pattern are probably due to the same process as the depression of hearing and increase in tinnitus. Instead of the toxic effect on the sensory cells of the crista in the production of vertigo he postulated that the localised distortions of the walls at the

points where the utricle joins the ampullae might be important. Such distortion when it occurs, might interfere with the mechanical action of the cupula and cause an imbalance between the canal and its mate of the other side, causing immediate vertigo. This explanation might explain why one particular canal might be the origin of the disturbance.

An interesting theory (Rollin, 1940) was put forward that the hearing changes might arise as the result of the distended saccule pressing upon the labyrinthine surface of the stapes and partially immobilising it, but Békésy showed in 1942 that increasing the intra-labyrinthine pressure did not interfere with the mobility of the stapes. The hearing loss with this type of stapes fixation would be likely to be conductive in type.

Lempert (1949) showed that increasing the intra-labyrinthine pressure up to 50 m.m. of mercury did not affect the cochlear potentials, though in this author's experiments the duration of the pressure increase was relatively short-lived. It is likely that increased pressure in the endolymph system would raise the

impedance in the vibratory mechanism so interfering with hearing in the early stages, though later structural disintegration of the organ of Corti may occur as the result of the pressure (Hallpike, 1938).

Subepithelial vesiculation has long been known to occur in the labyrinth and Hallpike drew attention to this again in 1938, but as the phenomenon occurred so frequently in normal labyrinths he was disinclined to attach any significance to it in the etiology of Ménière's disease. (Fig. 22 p. 16)

In a later paper Lempert (1952) postulated that Ménière's disease was a chronic progressive herpetic neuritis of the vestibular labyrinth of toxic or of trophic type. Rupture of vesicles releases toxic fluid into the endolymph which progressively damages the organ of Corti.

Recently it has been shown (Perlman and Kimura, 1957) that with neither arterial nor venous obstruction of the vessels of the stria vascularis was there much change in the size of the endolymphatic space. Neither collapse nor dilatation of the cochlear duct was noted. Venous obstruction results in haemorrhage into the peri- and endo-lymphatic spaces, arterial obstruction produces swelling of the tectorial membrane and cupular substances and a much more severe and rapid change in the nerve fibres. If vascular obstruction is of importance in

Ménière's disease it is unlikely that an acute but rather a long drawn out partial or frequent short-lived spastic obstruction occurs. Changes as severe as those produced by Perlman and Kimura probably never occur in Ménière's disease.

Imbalance of the autonomic nervous system and, in particular, over-action of its sympathetic division has been put forward by various authors as a possible cause of Ménière's disease.

Garnett Passe (1953) claimed that other internal ear disorders such as tinnitus and perceptive deafness could also be caused by such an imbalance and he has reported a number of cases showing the beneficial results of cervical or cervico-dorsal sympathectomy in these conditions. Until recently there has been little experimental or histological evidence in support of this theory although there seems to be no doubt that the internal ear receives both parasympathetic and sympathetic nerve fibres. These presumably play some part in maintaining it in a normal physiological state, but their detailed function remains unknown.

The recent work of Fernandez (1951) shows that efferent

fibres, probably parasympathetic, reach the internal hair cells through Rasmussen's tract, the vestibulo-cochlear anastomosis (bundle of Oort) and the intra-ganglionic spiral fibres.

Parasympathetic fibres may also reach the internal ear through the glossopharyngeal, vagus and intermediate nerves and their connexions with the tympanic plexus and geniculate ganglion (Rambo, 1953). Racine (1942) and Agazzi (1945) have demonstrated fine fibres with the morphological characteristics of autonomic nerves running to the maculae and cristae. The sympathetic nerve fibres to the internal ear run with the internal auditory artery. Smith (1951) reports that in the guinea pig "the fibre bundles become smaller as they follow the artery up the modiolus, branches being sent out from the bundles to the artery and its primary and secondary tributaries. The nerve fibres were found on the coiled secondary branches of the cochlear artery, but no fibres were demonstrable with the arterioles radiating out in the bony partition or descending in the bone of the modiolus to the spiral lamina; neither were any nerve filaments observed with the

capillaries."

The autonomic nervous system is governed by centres in the hypothalamus and factors affecting this region may therefore influence the internal ear through the above-mentioned efferent channels.

Recently some more experimental investigations into this subject have been published. Seymour and Tappin (1953) in a series of experiments on cats showed that stimulation of the cervical sympathetic nerve trunk produced a diminution in size of the cochlear microphonic potentials. The potentials fell by about one-third of their original value, but some recovery occurred when the stimulation was stopped. Histological examination of the stimulated cochleae showed concavity of Reissner's membrane suggesting that there had been a diminution of the secretion of endolymph. There was also some evidence that the composition of the endolymph had been altered. No vascular changes could be demonstrated in the sections but in another series of experiments they were able to show changes in

the blood vessels of the living stria vascularis which they had exposed and examined under magnification. The vessels contracted on sympathetic stimulation though the contraction was not so well marked as in extra-cranial structures such as the mucous membrane of the bulla. The vessels also contracted when adrenalin was applied, while histamine and nicotinic acid caused vasodilatation. Seymour and Tappin came to the conclusion that autonomic imbalance produces definite histological changes and suggest that this imbalance is a definite entity in the production of some disorders of the internal ear.

On the other hand, Rambo and his associates (1953) failed to produce any changes in the internal ears of monkeys after completely interrupting either the parasympathetic or the sympathetic supply. In another experiment they did not observe any dilatation of the blood vessels of the perilymphatic space after complete sympathetic denervation, although the vessels of the middle ear became widely dilated. Rambo and his associates concluded that there was no evidence that neurovascular

disturbances of the inner could be brought about by autonomic imbalance.

The autonomic imbalance theory of the causation of Ménière's disease must, therefore, still be regarded as unproved till further evidence is forthcoming. It seems, certain, however, from these experiments and from what is known of the effects of sympathectomy elsewhere in the body, that no lasting vasodilatation or paralysis of the vessel walls occurs in the cochlea after interrupting its sympathetic supply. In spite of this it seems likely that sympathectomy can influence pathological processes in the internal ear produced by causes other than autonomic imbalance since the range of response of the blood vessels is reduced after this operation. For example, in Raynaud's disease there is thought to be a "local fault" (Lewis, 1936) in the vessel walls themselves which makes them abnormally sensitive to cold and they will contract to this stimulus even when their nerve supply has been interrupted. The degree of spasm produced by cold is lessened after operation so that the patient is usually

considerably relieved of his symptoms. Similarly, if the hydrops of Ménière's disease is not due to autonomic imbalance, cervical sympathectomy could still be effective by preventing excessive reaction of the blood vessels to the exciting cause whether it be stress, allergy, metabolic disorder or vitamin deficiency. Whatever the cause may prove to be, it must surely work through the vascular supply to the internal ear.

Weille (1954) studied the spiral ligament and stria vascularis in live guinea pigs. When anaphylaxis was induced, the arterioles contracted tightly and they and the capillaries vanished completely from sight and the venules dilated. Aggregates of erythrocytes and emboli of highly refractile bodies were seen and also thrombi. On recovery, the circulation returned to normal, except for the thrombi. Thus vasoconstriction can occur in the internal ear under pathological conditions which is much greater than that produced in normal animals by sympathetic nerve stimulation. It does not appear likely that Ménière's disease is caused by vascular changes mediated through the sympathetic

nerves, otherwise section of these nerves should result in an immediate and complete cessation of attacks in all cases. Usually the patient experiences a few moderately severe attacks in the two or three weeks following operation, before the attacks become less frequent and less severe. It may be that some primary or local fault within the labyrinth produces its effect through the vascular supply to the inner ear and that sympathectomy, by modifying the power of the blood vessels to react, modifies the course of the disease without, however, affecting the primary course. Thus in Ménière's disease cutting off the sympathetic supply to the internal ear is unlikely to do more than stabilise the blood flow through the internal ear, probably by preventing extreme vasoconstriction.

Allergy. The disease has for many years attracted the attention of allergists and numerous papers have appeared describing the relationship, an early contribution being one by Duke (1923). A vaso-motor disturbance caused by blood-borne irritants affecting the sympathetic nerves to the part or an

action of local tissue metabolites on the same nerves was postulated by Mogan (1945). But although a great deal of discussion has been devoted to the conception that Ménière's disease is due to allergy there is no direct evidence of this. The disease is not familial, it tends to occur in middle life, other allergic manifestations are not often found associated with it and attacks of vertigo are rare in allergy. The indirect evidence in favour of the condition being allergic in origin may be stated as follows:

the pathological process is said to be one of non-inflammatory extracellular oedema,

the symptoms, both cochlear and vestibular, are fluctuant, often deafness and tinnitus increase during an attack of vertigo, to improve in the interval.

The ultimate course of the disease is variable, some cases have attacks occurring at intervals of months or years, suffering little diminution of hearing, in others the disease is steadily progressive until, finally, complete deafness and an insensitive

labyrinth result in a cure of the vertigo. This variability has been put forward in favour of a reversible mechanism that might well be allergic. But only a few actual instances of antigen-antibody type of allergy have been recorded. For this reason Williams (1944, 1947) suggested that some form of intrinsic or physical allergy existed. By this he meant the type first postulated by Duke (1925) in which there is no antigen-antibody reaction, but instead a sensitivity to heat, cold, atmospheric pressure, or to endocrine or emotional factors. Lindsay (1942) considered the evidence insufficient to suggest that Ménière's disease was allergic in origin and that there were many factors clinically against this aetiology.

Further aspects of this problem will be dealt with in the section devoted to medical treatment of the disease.

Atkinson (1940, 1941, 1942, 1943, 1944) approached the subject from a different angle. He suggested that Ménière's disease was a syndrome which can be produced by at least two causes. It was a vasomotor disturbance which in one group of

cases was allergic in origin and in the other was due to vasospasm. But he was able to demonstrate hypersensitivity in only two of his cases in the allergic group. He argued that, as it was well known that the final results of allergy in the tissues were due to the liberation of a histamine-like substance, then increased sensitivity to intradermally injected histamine should be a general indication of the presence of allergy. The supposition was based on the work of Dzsinich and Gallé (1939) who used injection of histamine in cases of asthma. These authors stated that it was possible to desensitise the tissues to histamine by graded injection of that substance. In 1940 Sheldon and Horton presented a preliminary report on the treatment of eleven cases of Ménière's syndrome with histamine with dramatic results, which is of course understandable when it is realised that the attack of vertigo is so short-lived. Atkinson adopted the test of Dzsinich and Gallé using an intradermal injection of 0.01 mgm. of histamine dihydrochloride in 0.1 gram of saline. His patients fell into two groups:

histamine sensitive (20%) and histamine insensitive (80%) as a result of the test. The former group of cases responded well to desensitisation with histamine, in the latter Atkinson suggested the symptoms were due to vasospasm. These he treated with nicotinic acid, a vasodilator.

Williams (1944) criticised this theory on the ground that he had seen equally good results in both groups with nicotinic acid, while Rainey (1945), Lillie (1944) and Hallpike and Harrison (Harrison 1945) obtained good results with histamine only. Farmer (1945) was quite unable to agree that allergic individuals were more sensitive to histamine than normal persons and concluded that the test was valueless in this respect. But this criticism had already been anticipated by Atkinson (1943), who withdrew the statement that the test was a true indicator of allergy, but insisted that its results were valid in dividing patients with Ménière's disease into two groups. Atkinson (1945) then gave more details of his test and emphasised that it was valid only if it were strictly

adhered to. Confirmation of Atkinson's opinion was given by Kodicek (1950).

The theory and corresponding method of treatment were based on the assumption that in a proportion of patient's with Ménière's disease there exists a state of abnormal sensitivity to histamine which can be recognised by an abnormal skin response. Haggie (1951) was the first to publish figures of the skin response of normal persons by this method. He found no significant difference in the response to histamine skin tests between 50 cases of Ménière's disease and 50 controls. Harrison (1951) found that the only value of the skin test was that it gave some indication of the patient's sensitivity to histamine and thus of the dosage of this drug required for treatment. He stated that the patients who respond to histamine injections respond almost equally well to oral nicotinic acid.

Types of Lesions. The results of the caloric tests, carried out according to the technique of Fitzgerald and Hallpike, were studied in a large series of normal subjects

by Hallpike, Harrison and Slater. Their findings were published in 1951. In respect to both canal paresis and directional preponderance the distribution curves were shown to have normal Gaussian characteristics with mean values of 0, and standard deviations, having the reasonably low value in each case of 15 seconds. These results have been confirmed by similar statistical analyses carried out by Petermann (1953), of Zurich and by Thomsen (1953), of Copenhagen, and the data in general provide a very satisfactory basis for the interpretation of the caloric test findings in abnormal subjects.

Investigations have been carried out on 429 characteristic cases of Ménière's disease. The results of the caloric tests are summarised as follows:

Unilateral abnormalities (370)	88%
Canal paresis (231)	55%
Directional preponderance to the unaffected side (106)	25%
Combined lesions (33)	8%
Bilateral abnormalities (40)	10%
Normal responses (7)	2%
Tests not completed (12)	

<u>Caloric Test Results</u>	M.S.H.	Hallpike's (1942) Series	Cawthorne's (1954) Series	De Kleyn
Unilateral abnormalities	88%	88%	91%	
Canal paresis	55%	49%	71%	73%
Directional preponderance	25%	21%	8%	11%
Combined lesions	8%	18%	12%	
Bilateral abnormalities	10%	-	-	
Normal responses	2%	12%	6%	

**Laterality in 417 cases of
Meniere's Disease:-**

		Cawthorne's (1954) Series
Left ear	54% (222)	45% (408)
Right ear	34% (148)	41% (371)
Both ears	10% (40)	13% (117)
Normal responses	2% (7)	

	0-20	21-30	31-40	41-50	51-60	61-70	+70	Total	Cawthorne's (1954) Series
Males	5	16	36	55	70	30	7	219 (51%)	489 (54%)
Females	10	13	35	59	52	34	7	210 (49%)	411 (46%)
Total	15	29	71	114	122	64	14	429	900

Classification of 648 cases of vertigo:-

		Cawthorne's (1954) Series
Ménière's disease	429	1,169
Positional vertigo	161	130
Vestibular neuronitis	52	152
Unclassified	6	115

A point of importance has been the remarkable constancy of the test results obtained with repeated tests on particular subjects carried out over a period of years. Thus, a canal paresis would generally remain constant or increase in degree. In a number of instances, however, the patterns of the caloric tests have been found to vary throughout the course of the disease. Thus, on one occasion directional preponderance alone may be present to the unaffected side; on another, canal paresis. On other occasions the two are found in combination. Nevertheless, the test results, when interpreted in accordance with the principle outlined above, have continued throughout to indicate a lesion of the affected labyrinth.

It is interesting to compare the numbers of different types of vertigo occurring in clinical ~~and~~ otological practice. Investigations have been carried out on 429 characteristic cases of Ménière's disease. 219 (51%) of these cases were male. In 222 (54%) the left ear was affected and in 148 (34%) the right ear was affected. The age incidence figures are attached.

During the same period 161 cases with positional vertigo were seen. In 29 of these the vertigo was central in type and in 132 the diagnosis of benign paroxysmal positional vertigo was made. Of ~~52~~ these cases 72 (55%) were male. Of the 132 cases of benign type of vertigo the sex distribution was as attached.

Again during this period 52 cases of vestibular neuronitis (perhaps better known as 'epidemic vertigo') were examined. 32 of these cases were male. A table showing the age distribution is attached.

Positional Vertigo

	0-20	21-30	31-40	41-50	51-60	61-70	+70	Total
Males	1	2	12	21	25	9	2	72
Females	1	4	5	17	21	12	-	60
Total	2	6	17	38	46	21	2	132

Vestibular Neuronitis

	0-20	21-30	31-40	41-50	51-60	61-70	+70	Total
Males	1	3	9	11	7	2	-	33
Females	1	1	7	1	6	3	-	19
Total	2	4	16	12	13	5	-	52

Aschan and Stahle (1957) have recently approached the question of the site of the lesion in Ménière's disease from an original angle, the analysis of electroencephalographic and nystagmographic records taken in cases of Ménière's disease. The authors state that the nystagmus patterns are not uniform. A continuous type of positional nystagmus (Dix and Hallpike 1952, Harrison 1956) (Direction changing of Nylen (1950) and Lindsey (1951)) which is usually central in type, was present in 5 out of 21 cases. Aschan has observed a marked similarity between the positional nystagmus of alcoholic type which is the result of the release of the central control of the labyrinth and that which he has noted in cases of Ménière's disease. The fact that destruction of the labyrinth relieves the vertiginous attacks does not necessarily mean that the lesion is central. Electroencephalographic recordings taken at the climax of the attack were abnormal in several cases of Ménière's disease, though not in 5 cases with positional nystagmus. Nystagmography demonstrates that the latent

nystagmus may continue at times for several months as a silent chronic vestibular disturbance.

The labyrinthine fluids

Our knowledge of the nature and function of the labyrinthine fluids until quite recently was based chiefly upon the anatomical data found in the well-known atlas of Retzius (1881). It was believed that the perilymph spaces, connected through the cochlear aqueduct with the cerebro-spinal subarachnoid cistern, were in effect a diverticulum of the latter in which was immersed the closed sac of the membranous labyrinth, derived from the invaginated ectoderm of the otic vesicle and filled with fluid of its own, the endolymph.

A more complete picture has gradually evolved, Waltner (1948) and many others have described a limiting membrane, from the arachnoidal web, which bars the labyrinthine opening of the aqueduct. The source and circulation of the endolymph was described by Shambaugh (1908). He considered it was secreted by the stria vascularis in the outer wall of the scala media of the cochlea.

Guild (1927) carried the investigations further by the injection of solutions into the guinea pig's endolymph system and showed that it was likely that a current flowed from the cochlea duct to the saccule and finally through the wall of the saccus endolymphaticus. Histological studies have been made of certain similar disorders of the inner ear having in common a localised degeneration of the endolymph system of the cochlea and saccule, this occurs in Ménière's disease, the so-called cochleo-saccular degeneration of Scheibe and in association with inherited forms of inner ear deafness observed in certain breeds of white cats, white bull terriers and mice. In all these conditions the degenerative changes in the cochlear end-organs are accompanied by changes in the stria vascularis and the parallel course of their development was demonstrated with particular clarity in the shaker mouse (Gruneberg 1940). The fluid spaces and sense organs of the utricle and semicircular canals are very little affected in any of these conditions. These findings were said to provide strong supporting evidence that the endolymph is secreted by the stria vascularis and is further responsible for the maintenance

of the metabolic processes of Corti's organ. There is still a great deal of controversy as to the circulation, nature and function of the labyrinthine fluids. The perilymph is not difficult to obtain in sufficient quantities to analyse, but much greater technical difficulties have been encountered in obtaining samples of endolymph which in addition must be small and accordingly particularly difficult to examine chemically. Measurements of the osmotic pressure of the labyrinthine fluids were reported in 1940 by Aldred followed by the valuable studies of Ledoux (1941, 1943 and 1950) of the physical and chemical properties of these fluids. More recently a detailed account of modern microchemical measurements of the electrolyte contents of the labyrinthine fluids of the guinea pig and cat have been provided by Smith (1954) and Citron (1956).

The fact that the protein content of the perilymph is higher than that of the cerebro-spinal fluid has an obvious bearing upon current views on the interchange of these fluids thought to take place through the cochlear aqueduct and may confirm the existence of the semi-permeable barrier mentioned above which retains the large protein

Analysis of Labyrinthine Fluids in the cat and guinea-pig:
Results of previous investigations.

Animal	Properties and Constituents	Spinal fluid	Perilymph	Endolymph	Reference
Cat	Osmotic pressure (g. NaCl/100g. H ₂ O)	1.017	1.046	1.058	Alfred, Hallpike & Ledoux (1940)
	Index of refraction ($n_D^{20.0}$)	1.33435	1.33495	1.33455	Ledoux (1941)
	pH.	7.45	7.87	7.82	Ledoux (1943)
	Chloride (m-equiv./l)	152	158	151	Ledoux (1950)
	CO ₂ (vol./100ml. s.t.p.)	43.2	32.0	31.5	
	Protein (mg./100g.)	31	268	118	
Guinea-pig	Sodium (m-equiv./l)	152	150	16	Smith, Lowry & Wu (1954)
	Potassium (m-equiv. /l.)	4.2	4.8	144	
	Chloride (m-equiv. /l.)	122	121.5	107	

Analysis of Labyrinthine Fluids in the Guinea-pig:
(Citron, Exley & Hallpike, 1956)

Constituent	Serum	Spinal Fluid	Perilymph	Utricular Endolymph
Sodium (m-equiv./l.)	140 (4)	150 (12)	148 (12)	26 (8)
Potassium (m-equiv./l.)	4.5 (4)	4.0 (12)	5.0 (12)	142.0 (9)
Chloride (m-equiv./l.)	-	122 (9)	120 (9)	110 (3)
Protein (mg./100g.)	-	20 (6)	75 (6)	25 (6)
Non-protein nitrogen (mg./100g.)	-	21 (6)	20 (6)	21.5 (6)

Analysis of Labyrinthine Fluids in the Cat:
(Citron, Exley & Hallpike, 1956)

Constituent	Serum	Spinal Fluid	Perilymph	Cochlear Endolymph
Sodium (m-equiv./l.)	155 (12)	162 (12)	164 (12)	66 (12) *
Potassium (m-equiv./l.)	6.7 (12)	5.9 (12)	6.0 (12)	117.0 (12) *
Chloride (m-equiv./l.)	-	150 (4)	150 (4)	-
Protein (mg./100g.)	-	25 (5)	142 (5)	-
Non-protein nitrogen (mg./100g.)	-	20 (5)	21 (5)	-

* In many of these samples the Na⁺ and K⁺ concentrations suggested contamination with perilymph. Three samples, however, showed the high values for K given in the table.

molecules withⁱⁿ the perilymph, while permitting interchange of the smaller electrolytes. The high protein content of the perilymph has on the other hand been explained as a stagnation phenomenon similar to that occurring in the subarachnoid space in association with the localised restrictions in the circulation of the cerebro-spinal fluid with increase of its protein content. The high potassium and low sodium content of the endolymph are unique for extracellular fluids. This might seem to establish a biochemical similarity between the endolymph and other intracellular fluids elsewhere in the body and it has been supposed that the endolymph is produced by secretory activity of some specialised cells. Smith (1954) notes the difficulties of nerve impulse transmission along un-medullated nerve fibres which traverse the tunnel of Corti's organ apparently immersed in the endolymph. Citron (1956) suggests that it is possible that the fluid system within Corti's organ itself is an enclave separated from the endolymph space, containing fluid with biochemical properties which do not differ from those of extracellular fluids surrounding nerve fibres in other parts of the body.

Biochemical

The publications of Mygind and Derderding (1929, 1938, 1943) have constituted the first biochemical approach of note to the problem. They started with the premise that the disease resembles glaucoma and is a hydrops of the labyrinth, originating they postulated, in a nutritional disturbance produced by capillary dysfunction with a resultant defective oxidation and increase in water-binding efficiency in the cells with subsequent intracellular oedema. They succeeded in relieving many cases, but the treatment did not strike at the origin of the trouble, namely, the cause of the localized accumulation of fluid in the labyrinths of patients with an otherwise normal metabolism. However, this was a break with surgical tradition and an impetus was given to thought and experiment along new lines.

Furstenberg and his colleagues (1934, 1936) reinvestigated the problem and produced evidence which indicated that a retention of sodium salts was of greater pathological

significance than a retention of water in the production of symptoms. The concentration of electrolytes and the degree of hydration of the blood was not reported in any of these communications, and it was left to Talbott and Brown (1940) to show that in four patients during an attack the serum potassium was raised and the sodium was lowered, whereas in forty-four patients between attacks the concentrations of sodium, potassium, calcium, chlorides, carbon dioxide, phosphate, protein and non-protein nitrogen were normal, and there was no change in the acid base equilibrium of the blood in Ménière's disease. They administered sodium salts, including the bicarbonate, orally and parenterally without precipitating an attack. They concluded that the idea must be abandoned, that the symptoms were due to gross retention in the body of water or of sodium chloride, because, if such were so, changes - not in practice found - would be present in the relative concentrations of sodium, protein and water in the plasma. This conclusion is, however, open to the criticism that it makes no allowance for

the equilibrating changes which may take place between these plasma constituents and the total body pools. Talbott and Brown (1940) explained the clinical benefits of their diet by stressing the importance of the potassium content of the blood, since it has been observed to vary in certain diseases in which the conduction of nerve impulses is disturbed. Normally the proportions of sodium and potassium in the diet are equal, but a relative increase in the potassium is inevitable in Furstenberg's regime. Since this diet is effective they investigated the combination of a normal diet supplemented with extra potassium (6-10 gm. equal, approximately to 80-134 m. e.g. potassium chloride daily), and found this an apparently successful method of therapy. Other authors, eg. Walsh and Adson (1940) have recorded similar results.

More recently Perlman et al (1953) found, in their series of cases with Ménière's symptomatology, that low serum sodium increased the intensity of the symptoms, and that raising the serum sodium concentration to normal relieved the condition.

Unfortunately, insufficient details of the examination of the patients treated by Perlman are available.

The variability of the results with different dietary regimes seemed to warrant a re-examination of the pathological and biochemical data on which the regimes have been based. In ordinary histological preparations from normal specimens the tectorial membrane is shown retracted from the organ of Corti, the separation being due presumably to the action of the fixatives, since in phase contrast examination the tectorial membrane is in contiguity with the hair cells and other elements of the organ of Corti (Kartsuki and Covell, 1953), ~~Perlman~~. ~~Perlman~~. In preparations, however, from cases of Ménière's disease, the tectorial membrane is flattened down on the organ of Corti, and this perhaps indicates that a firmer adhesion than normal has occurred between the two structures. Such adhesion cannot be attributed entirely to the increased pressure in the endolymphatic system since this pressure is acting all around the tectorial membrane. An alternative possibility is

that a change has occurred in the physicochemical nature of the tectorial membrane. This structure is either a glycoprotein (Wislocki and Ladman, 1955) or a muco-polysaccharide (Bélanger, 1953, Plotz, 1955) and may be expected to have some of the characteristics of a polyelectrolyte gel and to be influenced by the ionic nature and concentration of the surrounding medium. Crowe's (1938) interpretation of the dilatation of the endolymph system was that a continued secretion of endolymph of raised ionic concentration was possibly responsible for the increased fluid volume by water transfer from perilymph. This can hardly be so in that the production of a fluid of high osmotic tension requires more metabolic work to be done and this continuous increase of work is unlikely by damaged cells. The stria vascularis, considered to be the most probable site of formation of the endolymph, is least damaged in Ménière's disease and may therefore continue to secrete. However, the theory of increased osmotic tension demands increased secretory activity (of a fluid of high potassium content) and histologically no

confirmation - such as hypertrophy of the cells of the stria vascularis or of increase in its blood supply - has been noted. A further objection to the idea of the secretion of a fluid of high ionic concentration is that across a cell membrane of this nature transfer of water and ions is two-way, to attain the "steady state", and if extracellular pressure (hydrostatic and osmotic) increased on the cells of the stria vascularis, reabsorption of fluid cannot be considered improbable, providing the increased osmotic tension is due to small particles of the size of sodium and potassium ions. If a high osmotic tension is to be found in the endolymph in Ménière's disease, it is more likely to be associated with the breakdown of high molecular weight compounds to multiple particles of lower molecular weight, than with inorganic ions, and these substances would come from the obviously degenerating cells which are unable to perform the metabolic work necessary to maintain normal structure.

The part electrolytes might play in the causation or suppression of symptoms in Ménière's disease may still be of

considerable importance even if the osmotic changes and dilatation of the endolymphatic system are not primarily a matter of electrolyte secretion. Many workers have considered that patients with Ménière's disease were improved by loading the organism either orally or intravenously with sodium, or orally with potassium. The assumptions made were that body content of sodium and potassium could be significantly altered; that, with the dosages employed, the alteration could be maintained for long periods of time; and that changes, comparable to those produced in the body content of electrolytes, as indicated by plasma values, were effected also in the endolymph.

Since these experiments were performed more has been learned regarding the homeostasis of body electrolytes, particularly in relation to renal mechanisms and the influence of steroid hormones. Further, it is now known that the endolymph is an actively secreted fluid of a so-called "intracellular" character, i.e. having a high potassium concentration (Citron 1956) and

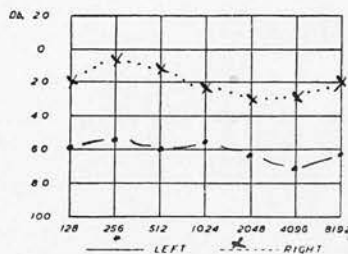
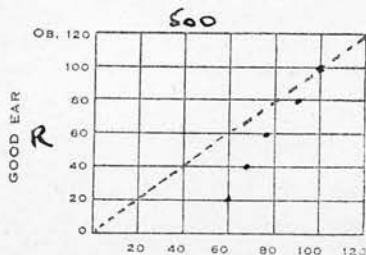
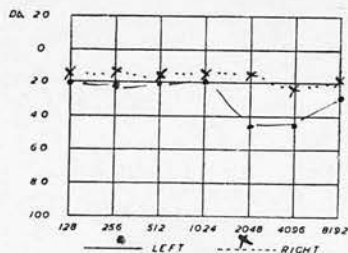
cannot be a plasma transudate influenced simply and directly by changes in plasma concentrations. Other points, which should be borne in mind when considering the possible inter-relations of electrolyte metabolism and Ménière's disease, are the difficulty of describing how a general body change, such as a change in plasma or body concentration of electrolytes, can produce a one-sided lesion unless there is also a local pathology; and, as a corollary, if indeed there be a "primary" pathology to be influenced by electrolyte changes, this influence will be at a maximum during acute episodes of the primary lesion and will be of less importance during quiescent periods, and, possibly, of little importance when the degenerative process has reached a more advanced and "stabilised" state.

It is possible, then, on the one hand, that the clinical improvement recorded in patients with Ménière's disease after treatment with, e.g. low dietary sodium, was dependent only on the fact that the patients concerned felt reassured that some real interest was being taken in their complaint and to that

extent their confidence was restored. This restoration of confidence may be an important factor to be considered in assessing the onset of a remission. On the other hand, since, in some respect, there is a reciprocal sodium-potassium relationship in the body, in that a loading with one ion leads to the excretion of the other - termed the "Bunge phenomenon" by Gamble (1951) - the improved clinical condition resulting from a low sodium diet, i.e. a relative potassium loading, could possibly be equally achieved by a high potassium loading and a normal sodium intake. It is not unlikely that repeated acute episodes, involving vomiting attacks with concomitant urinary loss of potassium, may result in a state of chronic potassium deficiency. Even without actual vomiting the anxiety state with attacks of vertigo may cause increased adrenal activity and potassium excretion. The correction of potassium depletion could, by itself, account for some of the increased feeling of wellbeing experienced by patients to whom this treatment has been given.

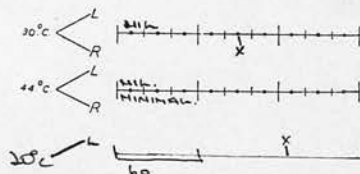
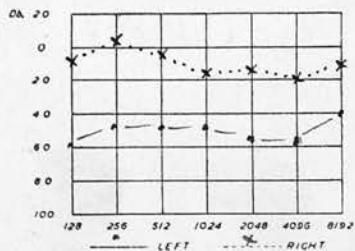


Low sodium intake and high potassium supplement have been the most widely practised forms of dietary treatment and, as a first step in assessing their value, we undertook experiments involving ion loading and depletion, observations being made clinically to determine either improvement or increase in intensity of the symptoms. Preliminary results are presented of experiments on two patients in whom the diagnosis of Ménière's disease had been established and who were experiencing very frequent vertiginous attacks. Though Ménière's disease is a relatively common condition it is infrequent to find a patient having very frequent attacks as was necessary at the commencement of this investigation. It was decided, thus, to undertake a particularly detailed investigation of the following two patients only, in the first stage of this investigation. Thereafter it would, we considered, be reasonable to continue the work on a number of cases of Ménière's disease with less frequent attacks, as out-patients. The results of this preliminary investigation are presented here. The second stage of the investigation is proceeding.



Difference Limen:-

	Right		Left	
	+ 10 Db.	+ 40 Db.	+ 10 Db.	+ 25 Db.
125	.25	.25	.0	.0
250	1.0	.5	.25	.0
500	.0	.0	.75	.0
1000	1.25	.25	.0	.0
2000	1.25	.75	.25	.25
4000	1.25	1.00	.75	.5
8000	2.0	1.25	.5	.25



Case A.

Patient first seen in March 1950 on account of frequent attacks of rotational vertigo which had been present intermittently for seven years. The patient was complaining of buzzing tinnitus in the left ear with some deafness on that side. She vomited with the attacks and was unsteady for a few days afterwards. The symptoms continued, though less severely, with sedation, and the patient returned in April 1956 complaining of very frequent severe attacks three or four times weekly, and loud tinnitus. Caloric test showed some left-sided deficiency. The patient was referred to Dr. C. S. Hallpike's clinic for confirmation of the diagnosis.

Loudness balance tests revealed complete recruitment of loudness of the left ear at 512 and incomplete at 1024 and 2048 probably owing to the little deafness which was present in the right ear. Investigation of the deafness on the right side by special tests showed that loudness recruitment was present on that side also. The caloric and loudness balance tests showed

the patient to be suffering from bilateral Ménière's disease, but it was felt inadvisable to carry out destructive surgery.

There appeared to be little doubt that the patient was suffering from Ménière's disease and in view of the frequency of the attacks it was decided to investigate her response to salt and fluid restriction. Throughout the course of the changes in diet there was no appreciable change in the audiometric recordings of the hearing, which were carried out on fourteen occasions.

Case B.

Patient first seen on 21.6.56. suffering from attacks of rotational vertigo and vomiting of some months duration, the attacks usually lasting two hours or so. She had had deafness and buzzing tinnitus in the left ear for about a year. Treatment with nicotinic acid tablets failed to relieve the condition. The ears, nose and throat were healthy on examination.

<u>O.E.</u>	Hearing		Right	Left	
	Rinne		pos.	pos.	
	Weber		←-----		} 512
	A.B.C.		↓ 7 secs.	↓	

Active corneals.

No spontaneous nystagmus.

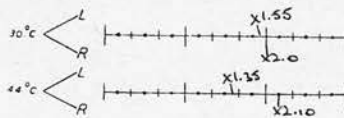
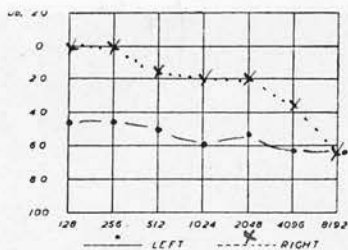
No positional nystagmus.

Steady on Romberg's test.

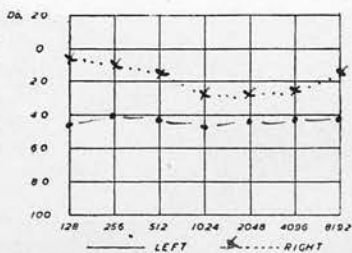
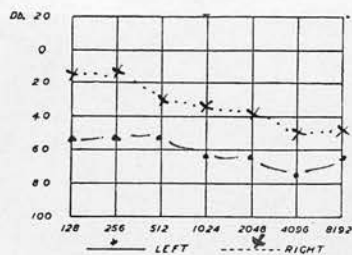
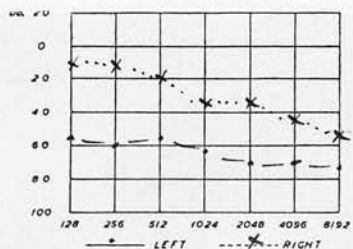
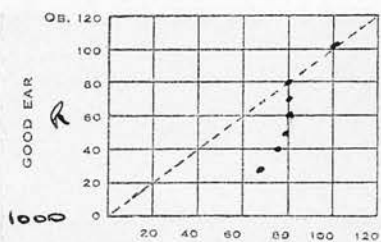
X-ray of sinuses - clear.

W.R., Kahn and Meinicke - negative.

In April 1957 the patient's response to medical treatment with sedation and vasodilators was not very satisfactory and she was admitted as she was having frequent attacks, two or three times weekly, for biochemical investigation. During the course of the investigation repeated audiograms were carried out and showed little variation of note in the hearing.



L.C.



Methods. The patients were allowed either ordinary ward diet or were given a "low salt" diet, i.e. an ordinary diet from which salt had been excluded in the cooking and to which no table salt was added. The patients chosen were intelligent and co-operative and made the effort to eat the same volume of food each day at the same time of day. This was necessary since in these preliminary experiments food sampling was carried out only four times for each patient, twice on normal diet and twice on the "low salt" diet. As a first approximation this was thought to be sufficient as it was hoped by various other means to effect changes in body balance and content of sodium and potassium far greater in extent than occurs with daily fluctuations. The various supplements and drugs used are given in tables A and B. The experiments were continuous in each patient, i.e. the dietary periods followed each other without a break for ^{over}~~some~~ thirty days. Urine was collected in 24-hour periods throughout the entire experiment and analysed for sodium and potassium content by flame photometry. The start of a dietary period was timed to

coincide with the start of a new 24-hour urine collection period.

Food was collected for an entire day, on each sampling occasion, by the method of measuring what the patient ate of each dish and placing an equal quantity in the receiver for homogenisation. The total day's food and drink was homogenised to a fluid smooth enough to be pipetted and quadruplicate samples taken off into weighed evaporating basins. The total homogenate was also weighed. In the first trials the samples were taken to dryness, under an infra-red lamp, carefully ashed with sulphuric or nitric acid and the digest suitably diluted for the estimation of sodium and potassium by flame photometry. Later food analyses were done by wet digestion of the samples with sulphuric or nitric acid since this method gave more consistent results in addition and recovery experiments.

Loss of sodium and potassium in the faeces was neglected except for the resin periods, in case B. The loss of ions by this route was calculated from data on average "in vivo" exchange rates given by other workers.

(Footnote)(This data was kindly provided by the resin manufacturers, Messrs. Bayer Products Ltd., Kingston-on-Thames, Surrey.)

Results. The results are given in Tables A and B and show the cumulative balance for each ion by the end of each dietary period as well as the overall balance for the whole experimental period. After a short preliminary period on ordinary ward diet the assumption was made that a state of ion balance had been achieved. This is a purely arbitrary assumption and, as pointed out below, may well not have been true.

Discussion. Table A. The continued loss of sodium during Period 5 would seem to require explanation. One possibility may lie in the form in which the potassium was administered. If the administered potassium were displacing cellular sodium - and no evidence of dehydration appeared - the return to ordinary diet and normal sodium intake would, in the first place, not influence extra cellular sodium^{and}/expansion of extra cellular fluid^{volume}/did not, in fact, occur until Period 8 when a definite increase in weight took place. However, the avidity which this patient's tissues had for K⁺ both in uptake and retention would suggest that the

TABLE A

	<u>Dietary Period</u>	Cumulative Balance to end of period		Electrolyte imbalance measured as divergence of Na & K. changes. m.eq.
		Na. m.eq.	K. m.eq.	
1.	6 days: average mixed diet 85 m.eq. Na.) 48 m.eq. K.)	0	0	0
2.	4 days: ordinary diet + supplement of 160 m.eq. K+	-128	+257	385
3.	4 days: low Na diet + supplement of 160 m.eq. K+ (48 m.eq. Na.)	-285	+396	681
4.	3 days: low Na diet + Diamox + 160 m.eq. K+	-450	+434	884
5.	4 days: ordinary diet	-598	+420	1018
6.	5 days: ordinary diet + 85 m.eq. Na+ (as NaCl)	-423	+418	841
7.	2 days: ordinary diet + 85 m.eq. Na+ (as NaCl) + 30 m.eq. Na+ (as citrate)	-396	+428	824
8.	8 days: ordinary diet + 85 m.eq. Na+ (as NaCl) + 30 m.eq. Na+ (as citrate) + 2 mg. DOCA. 1M daily.	-131	+468	599

arbitrary zero set at the end of the six days mixed diet might in fact have been a state of chronic negative potassium and positive sodium balance. The figures recorded up to the end of Period 7 would then be a record of fluctuations towards a more normal state of balance. Even with these assumptions the failure to excrete potassium while retaining sodium under the influence of DOCA is still not clearly explained. It should be emphasised that the patient became progressively better (subjectively) on this treatment and stated she had never felt so fit^{as}/at the end of the course, and has remained well since.

Dietary Period	TABLE B		Electrolyte imbalance measured as divergence of Na & K. changes. m.eq.	Body weight (kilos)	Plasma Values	Body Weight (Kilos)
	Na. m.eq.	K. m.eq.		m.eq.		
1. 4 days: average mixed ward diet (75 m.eq. Na.) (48 m.eq. K.)	0	0	0	Na-138 K-3.85		
2. 2 days: average diet + 85 m.eq. Na (as NaCl)	+135	-14	149			
3. 6 days: ordinary diet + 85 m.eq. NaCl + 30 m.eq. Na (as citrate) + 2 mgm DOCA. 1m. daily.	+165	-87	252	Na-143 K-3.7 Na-143 K-3.55		
4. 4 days: ordinary diet + 85 m.eq. NaCl + 30 m.eq. Na (as citrate) + 2 mgm DOCA. 1m. daily + ("Resonium A") sodium cycle resin 15 gm. 4 times daily: calculated as 100 m.eq. exchanged.	+354	-521	875	Na-143 K-3.28 (Wt incr. = 2.7 Kg.)		Weight incr. = 2.7 Kg.
5. 6 days: ordinary diet only	-406	-338	68	Na-143 K-3.93		
6. 2 days: ordinary diet + supplement of 160 m.eq. K	-547	-232	315	slow return to orig. body wt noted at start of exp..		slow return to orig. body wt noted at start of exp..
7. 2 days: low Na diet + 160 m.eq. K. (48 m.eq. Na)	-602	-170	432			
8. 2 days: low Na diet + 160 m.eq. K. + Diamox	-691	-217	474			
9. 1 day: low Na diet + 160 m.eq. K + (Kationium) K cycle resin 15 gm. 3 times daily: calculated as 50 m.eq. K exchanged.	-749	-159	590			
10. 3 days: low Na diet + 160 m.eq. K + 50 m.eq. exchanged from resin + Diamox	-843	+207	1050	Na-138 K-4.00		

Table B. As in Table A care has been taken to underestimate the extent of the changes. A definite sodium loading was achieved followed by a significant sodium deficit. The final recorded deficit of -843 m.eq. is approaching half the value for total extracellular sodium of the body, but no suggestion of dehydration was to be noted. So far from any discomfort, the patient volunteered to having felt better than for some time past.

The two experiments taken together demonstrate large, fairly acute, fluctuations of body electrolyte content, with both sodium and potassium in excess and in deficit, without the precipitation of any symptom of Ménière's disease; further it would seem reasonable to conclude that if it required these severe measures to enforce significant changes in body balance and content of the electrolytes, it is unlikely that the more gentle treatment of low sodium diet or a moderate potassium chloride supplement would influence homeostasis for any considerable period of time.

One suggestion, however, remains; as mentioned before the patient whose data are recorded in Table A might have been in

The potassium supplement was given in 2 to 3 hourly doses throughout the waking day. It consisted of a solution of KCl, KH_2PO_4 , K_2HPO_4 , KHCO_3 , the KHCO_3 (100 m.eq. K) being first nearly neutralised with L-glutamic acid. 25 gm. glucose was incorporated in the daily dose volume. The idea of using glutamic acid as a "K⁺-carrier" and glucose to prevent oxidation of the glutamic acid was derived from the work described by Krebs et al (1951). This mixture has proved to be acceptable and palatable by all patients who have been given it. The figures in the table, and previous experience, suggest that the K is in a form that is absorbed and retained to a greater extent than would be the case with KCl alone.

"Low Na" diet. No salt added during cooking or at table.

Diamox. 125 mgm at 6 a.m. and 125 mgm. at 12 noon, on each day of administration.

chronic negative potassium balance. The difficulty in the second experiment (Table B) of attaining a "good" response to DOCA alone, either in sodium retention or potassium excretion, again suggests a refractoriness which may perhaps have originated in a relative sodium excess and potassium deficit in the organism. One means of ~~t~~esting this hypothesis would be to measure the total exchangeable potassium of a series of Ménière's cases using ^{42}K .

No discussion on the movements of body sodium and potassium and the factors controlling the homeostasis of these electrolytes would be complete without mention of the part played by aldosterone. Although it is known that aldosterone is the principal adrenal steroid responsible for sodium conservation, and, to a lesser extent, potassium excretion, it is not known what controls the rate of secretion of aldosterone (Lancet 1957).

A description of the effects of changes in the dietary loading of electrolytes on the aldosterone output in the urine (and presumably, therefore, also on the rate of secretion of

aldosterone by the adrenals into the blood) has been given by Johnson et al (1957). From their own work and that of others they draw several conclusions which may be listed as follows:-

Normal subjects on an intake of normal diet except for

(1) sodium depletion, have an increased output of urinary aldosterone;

(2) sodium loading, have a decreased output of urinary aldosterone;

(3) potassium loading, have an increased output of urinary aldosterone;

(4) potassium depletion, have a marked decrease in the output of urinary aldosterone;

(5) potassium depletion + sodium deprivation, have a delayed increase in the output of urinary aldosterone, the increase not being as great as that observed during sodium deprivation alone;

(6) sodium restriction being maintained, but restoration of potassium to the diet, have a further slight to moderate

increase in urinary aldosterone over the output

recorded for condition (5).

These authors found that "relatively large changes in aldosterone output were observed without striking alterations in the concentration of plasma electrolytes, but the decreases or increases in aldosterone excretion after each change in the diet were in a direction favouring homeostasis of body sodium and potassium".

These observations and conclusions would appear to support the view that relatively small fluctuations of dietary intake of electrolytes, or the minor degree of sodium deficit produced by a " low salt" diet, would not by themselves be sufficient to alter the body balance of sodium and potassium to any significant extent.

Discussion of a new hypothesis.

Aldosterone exerts its principal effect, from the point of view of sodium conservation, on the renal tubule. The renal tubular cell has to perform enough work to transfer potassium

from the plasma to the urine and to move sodium in the opposite direction, both transfers taking place against concentration gradients. This work is done with a minimum of energy output by means of an ion exchange mechanism and it may be that one effect of aldosterone is to facilitate this work. The situation in the endolymphatic system could be of a similar nature. Elsewhere in the body extracellular secretions are usually of high sodium content, i.e. they are modifications of simple plasma transudates and osmotic and ion transfer work is kept to a minimum. Both endolymph and urine in certain circumstances have a high potassium content and a low, or relatively low, sodium concentration. So much is this the case with endolymph that it has been described as having an "intracellular" character. It is here suggested that it may be simpler to regard endolymph as starting out as a plasma transudate and that selective reabsorption and secretion by the stria vascularis alters the sodium and potassium concentrations. This hypothesis has the advantage of requiring no special work, or change, or new secretion, as regards non-protein

nitrogen, calcium and hexosamine, to produce endolymph from perilymph. There is the further advantage that it is simpler to conceive of an active circulation by this hypothesis. So long as endolymph is regarded as a secretion into a closed system there is difficulty in describing an adequate circulation in the absence of a drainage point or canal and no such exit has yet been noted. If, now, circulation is assumed to start from a plasma transudate, having the hydrostatic pressure of the general circulation to provide the energy, and this transudate is, or becomes, perilymph and passes through Reissner's membrane to become endolymph, it is possible to visualise a sufficiently dynamic flow as to bring oxygen in physical solution in adequate quantities to the cells of the organ of Corti. The special character of the endolymph would be maintained by selective absorption and secretion by the stria vascularis.

A number of observations and experiments will be cited in support of this concept, but it is strongly emphasised that the starting point of any theory of function, or of abnormality, of

the endolymphatic system must be the description of how oxygen reaches the organ of Corti. Perlman and Kimura (1957) state that within seconds after respiratory oxygen is replaced by nitrogen, or after general blood flow is impaired, functional changes are demonstrable in the labyrinth. It is reasonable to suppose from this short time relationship, that the cells to be first affected by anoxia will be those having a specialised function but furthest away from a good capillary network. Since histologically it is difficult to demonstrate any direct blood supply to the organ of Corti and since, from their situation and contiguity with the nerve endings of the auditory nerve, it may be assumed that Hensen's, Deiter's and the hair cells have an active metabolism and therefore require a steady oxygen supply, it seems fair to conclude that it is in the cells of the organ of Corti that the impaired functional changes occur in a matter of seconds when oxygen flow fails. The first requirement therefore of any theory of formation and circulation of endolymph must be a description of the direction of the oxygen gradient.

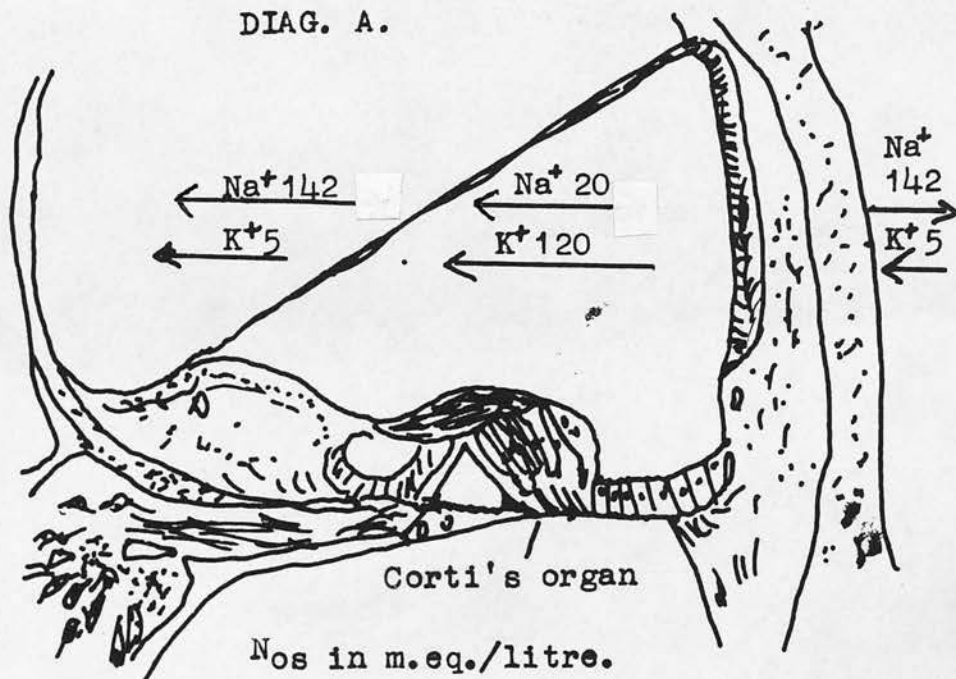
Formation of endolymph may occur in one of several structures. The stria vascularis is assumed by most authors to be the source of endolymph, but, as has been already remarked, no drainage canal has been described to permit of a circulation starting from the stria vascularis, and a reabsorption through some membrane must therefore be postulated. Citron and Exley (1957) have pointed out that active transport across Reissner's membrane would seem to be necessary in any theory, but this structure is not so situated or constructed as to make it satisfactory, either as a source or exit of a circulation. It could, nevertheless, effect the changes in concentrations of sodium and potassium to transform endolymph into perilymph. Perilymph would then drain to the cerebrospinal fluid, the high protein content of the former being diluted by the larger volume of the latter. Drainage of perilymph may also occur along lymphatics and Kley (1951) presents evidence suggesting that perineural flow and direct transudation of perilymph into the venous system are further possibilities.

There are serious objections to the theory of a circulation

beginning at the stria vascularis and passing through the stages of endolymph and perilymph. The least serious is the difference in protein concentrations. To make endolymph into perilymph Reissner's membrane would have to add protein. A more serious objection is the question of oxygenation. If the stria vascularis is to be the site of secretion of endolymph it is necessary to suppose that oxygen is passing through three layers of actively metabolising cells, i.e. cells having a large oxygen consumption. If, on the other hand, the stria vascularis is to be considered relatively inactive metabolically and allows to pass a plasma transudate rich in dissolved oxygen, then we have the anomalous position that Reissner's membrane, a thin endothelial structure without a very abundant blood supply, has all the work of ionic change to perform while the stria vascularis acts only as a mechanical filter though it possesses a rich capillary network underlying cells whose micro-anatomical structure resembles more the renal tubular cell than the glomerulus (Smith, 1957; Pease, 1956; Engstrom, 1955). An important point in connection with

oxygen supply is made by Perlman and Kimura (1957) who found, in experiments using guinea pigs, that anoxia of the cochlea and labyrinth, produced by obstruction of the inferior cochlear vein, led to profound disturbance of vestibular function with nystagmus, head and body torsion and circling movements. The animals were sacrificed at intervals after production of the lesion and the structures preserved by intravital perfusion of fixative. Histological examination showed that the stria was particularly susceptible, often being the first to show signs of damage. Dilatation of stria capillaries and oedema of the epithelium were noted one hour after venous obstruction. Within a few hours haemorrhage into the epithelium and into the scala media was noted. Disintegration of the epithelial layer of the stria soon followed in some (animals). On the other hand, within 24 hours after venous obstruction loss of outer hair cells was clearly evident, but the inner hair cells were more resistant and degenerative changes appeared after two days. This description, and examination of a photomicrograph of a preparation from one of the experiments

DIAG. A.



quoted indicate that the organ of Corti had survived several hours at least after disintegration of the stria vascularis had begun. This conclusion argues strongly that oxygen was reaching the organ~~of~~ Corti from a source other than the stria vascularis. It is worth emphasising that in this case the organ of Corti survived the destruction of the stria while a characteristic of Ménière's disease is that the stria remains intact while the organ of Corti degenerates. It is difficult to escape the conclusion that the organ of Corti is not dependent on the stria vascularis for its oxygen supply~~and~~ other nutriment.

Perhaps the most serious objection to the theory that the stria vascularis is the source of endolymph is that raised by a consideration of ion transport energetics. In Fig. A there is diagrammatically represented the ionic situation in the case of a flow from plasma through the stria vascularis to the scala media, from there through Reissner's membrane to the perilymphatic space. If the stria vascularis has actively to secrete K^+ and withhold Na^+ then it must do so, in this case,

without the use of an ion exchange mechanism. Since the flow is away from the stria vascularis no Na^+ can reach the endolymphatic surface of the strial cells to permit of an equimolar exchange of sodium and potassium with minimum energy expenditure. If a local transudation were occurring to provide sodium for reabsorption, the description of a circulation starting from the stria vascularis would no longer hold, since reabsorption would entail something of a reverse flow, or alternatively the correct description would be that of a transudate at the stria with the ionic work being done by Reissner's membrane because sodium in the strial transudate would immediately distribute throughout the endolymphatic space.

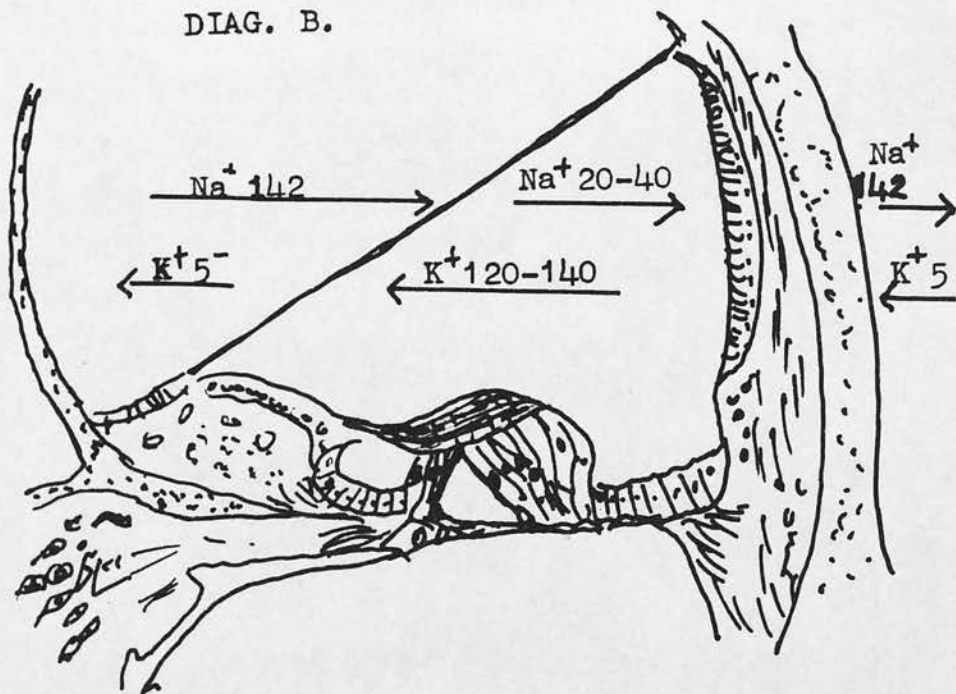
The other cation exchange which could occur to minimise energy expenditure is that of K^+ for H^+ . One must assume a blocking of Na^+ transport at the basal layer of the stria vascularis; the upper layers then have a carbonic anhydrase mechanism for forming and dissociating carbonic acid, thus providing ionised hydrogen. H^+ could then exchange for K^+ and

potassium bicarbonate would be secreted. Although the pH of endolymph is somewhat higher than that of plasma and this elevated pH could be explained by the secretion of potassium bicarbonate, the data of chemical analysis of the endolymph (Citron and Exley, 1957) do not support this idea. The endolymph has a low carbon dioxide content (Ledoux, 1950) and the exchange theory involving bicarbonate would require a high one. Further the chloride content of endolymph is high, i.e. of the same order as cerebrospinal fluid and perilymph and yet another ion exchange mechanism would be necessary to explain chloride transport after separation from sodium in the basal layer of the stria vascularis. The chloride content is best explained by assuming the formation of a plasma transudate, but as pointed out above, the formation of transudate only by the stria leaving the active ionic transport work to be done by Reissner's membrane is in contradiction to their obvious histological structures.

Fig. B presents a diagram of the ionic situation in the alternative case, i.e. the hypothesis suggested in this paper,

of flow proceeding from perilymph through Reissner's membrane to endolymph, the stria vascularis acting as a selective absorbing site. In this case Reissner's membrane has no external ionic work to do at all except to prevent the flow of K^+ from the scala media to the scala vestibuli. The reduction of protein concentration to produce endolymph from perilymph may be ascribed to membrane impermeability to large molecules. The stria vascularis, on this hypothesis, is presented ^{in the first instance} with a high sodium low potassium fluid, from which it extracts the sodium and exchanges potassium for it by an ion exchange system analogous to that of the renal tubular cell, using a minimum of energy. Since potassium is not to pass Reissner's membrane, except by a relatively slow equimolar exchange for sodium, i.e. at a rate suitable to meet the needs of the stria vascularis, potassium ^{until the required concentration is reached.} concentration in the scala media can build up. It should be noted that this hypothesis provides for the ionic work which has to be done against gradients, to be done by the structure capable of doing it, viz. the stria vascularis, while the

DIAG. B.



equimolar exchange of Na^+ for K^+ through Reissner's membrane takes place in the direction of the respective concentration gradients and hence requires no work on the part of the membrane. Osmotic pressure on both sides of Reissner's membrane is the same. No explanation is required for the concentrations of chloride, calcium, non-protein nitrogen and hexosamine since no change occurs in their concentrations, but it may be pointed out that this hypothesis shows an economy in the postulated number of secreting surfaces over other theories which require separate mechanisms to produce perilymph and endolymph, which have so many features in common.

If endolymph comes from perilymph it is necessary to enquire into the source, or sources, of perilymph. Kley (1951) performed experiments on guinea pigs in which he injected fluorescein into the blood stream after blocking the cochlear aqueduct to prevent access of cerebrospinal fluid. Fluorescence nevertheless appeared in the perilymph simultaneously with its appearance in the aqueous humour of the eye. He suggested that perilymph was formed by

ultrafiltration from the abundant vascularisation of the perilymphatic space. In the human subject this source may be of greater importance than in animals since the cochlear aqueduct in man is much less permeable than in animals. Altmann and Waltner (1950) working with rabbits, cats and monkeys, and using the method of Weed (1914) of injecting iron salts into the subarachnoid space, sacrificing the animals after several minutes and determining the distribution of the iron salts by the Prussian blue reaction, came to the conclusion that, although a process of diffusion carried the salts from the cerebrospinal fluid through the cochlear aqueduct to the perilymphatic spaces, no active fluid currents appeared to exist in either direction. Their evidence suggests that the main part of the perilymphatic fluid is formed in the perilymphatic space, i.e. in agreement with the work of Kley mentioned above. Notable support of this view is obtained from a consideration of the protein concentrations of cerebrospinal fluid, perilymph and endolymph. The protein concentration of perilymph is four or more times higher

than that of cerebrospinal fluid and also much higher than that of endolymph. Perilymph could thus not be formed from either cerebrospinal fluid or endolymph without further secretion, or alternatively reabsorption of all constituents except protein.

The evidence cited in the last paragraph provides a source of perilymph given the hypothesis that circulation in the fluids of the inner ear proceeds from perilymph to endolymph. That evidence suggests that perilymph is a plasma transudate formed on the scala vestibuli side of Reissner's membrane (or perhaps in the scala tympani on the lower side of the basilar membrane). This description permits the postulate to be made of an oxygen rich fluid having only a short distance to go to reach the organ of Corti, traversing only a membrane (Reissner's membrane) which is doing little or no external work.

This hypothesis thus takes account of the oxygen supply, requires a minimum number of exudative and absorptive surfaces, permits the description of a dynamic circulation using the hydrostatic pressure of the general circulation as a starting

point and requires the absolute minimum output of osmotic and ion transfer energy by the membrane cells concerned, allocating that work in accordance with their anatomical structure, and in accordance with the known ion concentration gradients.

Certain objections to this theory must be considered. Some experimental results (Guild, 1927; Altmann and Waltner, 1950) have been interpreted as meaning that injected granular material could be found in various parts of the scala media but seldom on the surface of the stria vascularis (Smith, 1957). Also cellular debris dislodged by acoustic trauma from the basilar membrane is rarely seen near the stria vascularis (Smith and Covell, quoted in Smith, 1957). This interpretation suggests that the endolymph is formed by the stria vascularis and washes away the granules. As far as Altmann and Waltner's experiments are concerned, they did not inject granular material but soluble iron salts which were later precipitated as Prussian blue in the sites to which the salts had been diffused or had been carried. Altmann and Waltner's results, so far from suggesting that a fluid outpouring was

washing away the granules from the stria vascularis, on the contrary suggest a rapid resorption of iron salts through the stria. They write, "Since salts are only resorbed in dissolved form together with fluids, fluid movements must exist, directed in the scalae towards the lower and upper parts of the spiral ligament, and in the cochlear duct towards the external spiral sulcus, the spiral ligament and the crista spiralis". However, they add that the fact that in their experiments the iron salts moved from the peri- into the endolymphatic space simply demonstrates the high degree of permeability of the membranes and should not be taken as an indication that this is the prevailing direction of movement of dissolved substances under physiological conditions. "Normally", they write, "it is more likely to be from the endolymph to the perilymph". Whatever the final interpretation of this work, it does not signify such a flow of endolymph from the stria as to sweep the soluble iron salts (not granules) away.

The problem of the accumulation of debris in other parts of the scala media, and elsewhere in the membranous labyrinth, but

not over the stria vascularis, must be examined. Waltner (1954) in his study of perilymph formation and composition found that on removal of perilymph through the round window membrane, a fibrinous precipitate formed in the endolymphatic space. He interpreted this to mean a sudden increase in production of endolymph as there was marked engorgement of the vessels which lead to the stria vascularis and occasional blood cells in the precipitate. On the other hand Perlman and Kimura (1957) in their study of experimental anoxia of the inner ear found that the stria vascularis was particularly susceptible and disintegration of the epithelial layer followed soon after production of the lesion. They found also dilatation of the strial capillaries. There seems no doubt that in the experiments of Perlman and Kimura the stria had ceased functioning and if, in Waltner's experiments, a reflex vascular disturbance resulted from the injury to the round window, then the picture of capillary engorgement, fibrinous exudate and occasional haemorrhage would be in agreement with the findings of Perlman and Kimura, i.e. a cessation and not an increase in activity of

the stria vascularis. The absence of debris in the vicinity of the normal stria vascularis may indicate not so much its power as a secretory membrane as its ability to absorb and phagocytose larger molecular aggregates.

A test of the validity of this new hypothesis of the physiology and biochemistry of the inner ear fluids would be to arrive, on the basis of its postulates, at a satisfactory explanation of pathological changes. The principal pathological finding in Ménière's disease is dilatation of the scala media. Other points are that the cells of the organ of Corti degenerate while the stria vascularis survives.

The problem of the dilatation of the membranous labyrinth has to be reconsidered in the light of recent work. Engstrom and Liden (1957) have described some observations and experiments which show that the tension and shape of the membranous labyrinth are to a great extent dependent on the support and pressure level of the perilymph. They would consider the perilymph and endolymph as two separate hydrodynamic systems separated by a thin resilient

wall. This could well be true of the semicircular canals (and perhaps of the utricle and saccule) but cannot be wholly true across Reissner's membrane. Their experiments do point to the possibility, taken together with the hypothesis put forward in this paper, that the dilatation of the membranous labyrinth in Ménière's disease could be due to a failure of perilymphatic pressure, while the active exchange of potassium for sodium in the scala media would mean the continuance of a normal, not an increased, osmotic tension in the endolymph. Thus the only pathological lesion required on the basis of this hypothesis would be a disturbance either of perilymph production in the vascular network of the perilymphatic space, or of perilymph absorption by routes other than towards endolymph. Production of perilymph could be interfered with by a process not amounting to fibrosis but akin to the thickening of the fibrillar material of the basement membrane seen in early glomerulonephritis, or by a one-sided lesion of the nervous system supplying the vessels of the perilymphatic space - not a neuritis, but an imbalance of

innervation leading to constriction of the arterioles.

Drainage of perilymph towards the spiral ligament in the outer two scalae of the cochlea and by the perilymphatic space of the vestibule and thus direct transudation to the venous system would seem to be highly probable. (Altmann and Waltner, 1950; Key, 1951). If this description of absorption of perilymph along the whole width of the spiral ligament is correct, then the relative pressures of endolymph and perilymph in the scalae will be at least partly dependent on the balance of absorption. This may seem speculative but it should be noted that the standard description of transmission of sound stimuli involves the conversion of vibrations in the oval window to fluid movements in the incompressible perilymph. This concept either entails a static fluid unchanging in volume, and probably in composition, with no inlet or outlet, or, since this is unlikely in a biological organism and improbable in any case for perilymph, it demands a dynamic flow with a system for balancing secretion and absorption. Equilibration of perilymph pressure with that of the

cerebrospinal fluid is conceivable in animals with a wide cochlear aqueduct, but in the human subject this explanation could not be sustained. An imbalance of absorption, such as an increase of leak-away from the outer scalae without a compensating increased rate of production of perilymph would lead to a relative, not absolute, increase in pressure in the scala media. The continuance of this trend could produce the symptomatology of Ménière's disease in that a drop in perilymphatic pressure would lead first to an apparent increase in volume of endolymph and later to a true increase. The apparent increase would occur on the basis of the model described by Engstrom and Liden; the later true increase would be due to the gradual accumulation of potassium, gradual because the rate of flow through Reissner's membrane would be diminished in proportion to the increased drain away in other directions, and accumulation because the stria vascularis in Ménière's disease remains unimpaired and, to begin with, Reissner's membrane would also be functionally intact. The pressure in the endolymph need not be altered from normal. Here

it is worth repeating that the organ of Corti can surely not be nourished from the stria vascularis since in Ménière's disease the stria remains intact while the organ of Corti degenerates. On the other hand, if the organ of Corti depends for its oxygen on perilymph, when the rate of flow through Reissner's membrane is diminishing due to reduced production of perilymph or to greater loss by other routes, then degeneration of the organ of Corti could be expected to result.

Another feature of Ménière's disease could be explained on this basis. As Reissner's membrane becomes more and more distended leakage, probably in sudden spurts, of endolymph might be expected to occur. This would have two results, firstly sharp, probably temporary, changes in labyrinthine pressures with ensuing vestibular stimulation, and secondly acute changes in the ionic composition of endolymph, raising sodium concentration and lowering the potassium, until the stria vascularis restored the situation. In so far as the ionic composition has a bearing on the structure and function of the tectorial membrane,

the very exposed and vulnerable hair cells and the unsheathed nerve endings of the auditory nerve, sudden changes in ion concentrations must be taken into account as sources of pathological irritation.

If this hypothesis of the physiology and biochemistry of the inner ear fluids has stood the test of permitting a correlated description of the pathology and symptomatology of Ménière's disease with the economy of one postulated lesion, these concepts could be put to the further tests of confirmation by animal experiment. The animal chosen should have a minimum of communication between perilymph and cerebrospinal fluid by means of an open cochlear aqueduct. Where a free communication between perilymph and cerebrospinal fluid exists there would probably be rapid equilibration of pressures and also an actual flow of fluid, and it might prove impossible to produce a sufficient imbalance of flow and pressures in the cochlea.

Another piece of information which would help to confirm the hypothesis being presented would be the finding, in a more

chronic state of Ménière's disease, of a raised sodium and lowered potassium concentration in the endolymph.

It is perhaps worth pointing out, in conclusion, that this new hypothesis has the merit of permitting a reconsideration of the value of treatment of Ménière's disease with vasodilating agents, e.g. nicotinic acid or histamine on a rational basis, in that the action of the vasodilator may be on the vessels serving the perilymphatic transudatory membranes. Also the question of dietary ion balance and the part possibly played by aldosterone could be reassessed against a background of a more closely detailed physiology. It is highly improbable, on our present knowledge, that any changes brought about by a low salt diet in the pathology underlying Ménière's disease, have anything to do with a genuine depletion of extracellular fluid, as a means of reducing endolymphatic oedema or hydrops. It is possible, however, to suggest a means whereby dietary ion balance might exert some influence. Making reference again to the work of Johnson et al (1957) mentioned earlier, it can be seen that aldosterone excretion

(and secretion) is increased both with sodium depletion and potassium loading. These effects have been described also by Luetscher and associates (1954, 1955). The dietary regimes advocated for Ménière's disease have been precisely those of sodium restriction and potassium loading. The first effect of increased aldosterone production would be to nullify the influence of the dietary changes on total body electrolytes, but if, as seems reasonable to suggest, aldosterone has an effect on the stria vascularis similar to that which it exerts on the renal tubule - since their cellular structure is similar and their function as regards potassium movement must be presumed similar on any hypothesis - then the effect of the dietary regimes, acting through aldosterone, would be to facilitate sodium reabsorption and potassium secretion by the stria vascularis. In this way dietary electrolyte treatment, at a suitably early stage of the disease, could ameliorate the symptoms of Ménière's disease by aiding in maintaining a normal ionic structure in the endolymph. The more rational procedure, if this is true, is to prescribe

potassium supplement rather than sodium restriction.

The site of origin and other factors in the physiology of the labyrinthine fluids is likely to have a considerable bearing on other pathological conditions of the labyrinth. In the cases of leukaemia of this organ already described it will be seen that white blood cells fill the perilymph spaces, but very few are to be seen in the endolymph. If endolymph were derived from the stria vascularis the endolymph space would probably be filled with the cells escaping from the vessels supplying the spiral ligament. If, on the other hand, perilymph is a transudate the cells would be held up almost completely by Reissner's membrane and the few passing this barrier would be rapidly absorbed by the macrophages of the stria vascularis. The changes found in the labyrinth as the result of rubella are likely to be toxic in origin and here changes occur in most of the elements of the scala media.

Treatment

Because of the normal remissions of Ménière's disease it is very difficult to assess the value of any therapeutic procedure. The objects of the therapy are to eliminate the vertiginous attacks, or, at least, to diminish their intensity and frequency and, if possible, to reverse the hearing loss. In the light of the spontaneous remissions of symptoms, an estimate of the efficacy of any therapy becomes a matter of clinical judgment and of observation over a considerable period of time. Yet it is interesting that excellent results have been claimed for the medical treatment of Ménière's disease in very many ways by competent otologists often due, as Fowler (1952) has emphasised, to the fact that some improvement almost invariably follows careful examination, especially if the patient is admitted to hospital, no matter what treatment be used. It is not unusual for a patient to find considerable improvement after caloric tests if he does not understand their aim. There appears to be little doubt that stress is an important factor in many cases of

Ménière's disease, it may be fatigue, the result of infection, or emotional stress, and that the symptoms occur after long continued aggravation of the stress in a susceptible individual. A medical adviser who can convey his confidence in any form of treatment will often enable this type of patient to develop a remission of vertiginous attacks at times for many months or years. Unfortunately most of these cases relapse eventually and require more medical or surgical treatment, but Fowler (1952) considers that psychotherapy or analysis will very much reduce the need for destruction of the labyrinth.

Fowler placed each of a series of cases of Ménière's disease into one of five groups, each demonstrating an outstanding life stress situation which preceded the attack: (1) personal antagonism, (2) sexual abstinence, (3) sexual conflicts, (4) death of a near relative and (5) various forms of life stress including surgical operation, tension with relatives and financial problems. In all groups patients demonstrated a lack of ability to cope with excessive tensions and direct release of

aggression through acceptable channels was blocked.

There can be no doubt that the patient is often in need of reassurance as he believes he has a cerebral tumour or some intracranial and intractable lesion. An explanation should be given of the aetiology and he must be given to understand that gradually, but with reasonable certainty, his vertigo can be overcome. Each case should be considered as an individual problem and the patient must understand that immediate and dramatic results are unlikely. An important factor in many patients is the profound mental disturbance resulting from the violence of the symptoms hence the importance of adequate sedation, at least until confidence is gained. Phenobarbitone, though non-specific, appears to discourage the spread of the disturbance caused by the attack to the rest of the brain, but it is depressing if used for long periods and one grain of sodium amytal each morning interferes less with the patient's feeling of wellbeing.

The effect of numerous compounds on the control of vertigo

was investigated by Chinn (1951) and those of the atropine series were found the best. Gay and Carliner (1950 and 1951) had previously reported that Dramamine (dimenhydrinate, B-dimethylaminoethyl benzohydryl ether 8 chlorotheophyllinate) had a marked curative effect on seasickness and also Benadryl was shown to have a similar effect. It was thus considered that the antihistamine property might be important, but others of this group were tried and some had little effect on vertigo so that the actual anti-histamine action was not effective. All active drugs have been shown to have an anticholinergic action (Chinn, 1950). Avomine (promethazine 8 chlorotheophyllinate) is a preparation similar in constitution and action to Dramamine. A more powerful preventative effect against seasickness than Dramamine is possessed by hyoscine, but better still hyoscine aminoxide has only one-sixth of its toxicity with one-third of its potency. Two mgms. daily may keep the patient free of attacks, but blurred vision and dryness of the throat still sometimes occur. Stemetil 1- $\bar{3}$ -(3-chloro-10-phenothiazinyl)

propyl-4-methyl-piperazine dimaleate has been introduced more recently, it resembles 'Largactil' (chlorpromazine) in the range of its pharmacological actions but it shows marked quantitative differences. Thus it is several times more active as an anti-emetic but less active in reducing conditioned and instinctive reflex activity, and in enhancing the actions of centrally active drugs such as hypnotics, anaesthetics and analgesics.

The Vasodilators. Histamine, nicotinic acid & Ronicol (B-pyridyl carbinol) appear to come under this heading. All produce a marked peripheral vaso-dilatation which doubtless convinces many patients of the efficacy of the treatment. There is some doubt as to the effect of the drugs on the intra-cranial and labyrinthine vessels. The use of histamine in the production of experimental peptic ulcer in animals may be the cause of misgivings over its use in the treatment of Ménière's disease, but Horton (1943) who used 14,700 injections, had seen only one acute ulcer from its use, and this cleared up rapidly. It occurred in a patient who had omitted to take a full meal before the injection;

Instructions for the House Surgeon and Sister.

INTRAVENOUS HISTAMINE.

It is advisable for the patient to take a full meal before the injection and the patient's sensitivity should be measured by the intradermal injection of 0.005 mgm. histamine acid phosphate (the solution usually prepared contains 1 mgm. per c.cm. and is diluted 1:10 for the intradermal test).

The treatment is begun by the intravenous injection of 1 mgm. of histamine base in 250 c.cm. saline, 5 per cent dextrose, or preferably 0.8 per cent potassium chloride over one-and-a-half hours, more or less, according to the sensitivity of the patient. The blood pressure must be watched during the operation and adrenaline should be available, although this is rarely necessary. The injection is repeated after forty-eight hours on one or more occasions. Thereafter subcutaneous or intramuscular histamine maintenance injections of 1 mgm. per c.cm. solution of histamine base are given weekly, beginning with 5 minims (0.3 c.cm.) and advancing the dose slowly up to 20 minims (1.2 c.cm.) according to the patient's response as measured by the flushing and feeling of heat.

328 injections had been used in one patient with no measurable defects. The patients' sensitivity to the drug is measured by the intradermal injection of 0.005 mg. histamine acid phosphate and the resultant reaction compared to that of a control of sterile water (Browne, 1942). As in other methods of treatment, the earlier in the course of the disease the therapy is instituted the more satisfactory the results are said to be. Deafness and tinnitus both may disappear in early cases; in 90 per cent. of all cases the patient, Lillie (1944) states, is free of vertigo.

Intravenous treatment is begun by the injection of 1 mg. of histamine base in 250 c.c. saline, 5 per cent. dextrose, or preferably 0.8 per cent. potassium chloride over one and a half hours, more or less, according to the sensitivity of the patient. The blood-pressure must be watched during the operation and adrenaline should be available, though this is rarely necessary. The injection is repeated after 48 hours on one or more occasions. Thereafter subcutaneous or intramuscular maintenance injections of 1:10,000 solution of histamine base are given weekly commencing

Outline of treatment with histamine solution as handed to patient's doctor, if treatment is advised out of hospital (Harrison 1947).

Standard Histamine Solution - 1 milligram per c.c.

The patient's sensitivity to this drug is tested by intradermal injection of one in ten dilution of the above in saline, with a saline control.

According to the size of the reaction to the intradermal test 2 to 5 minims of the standard solution is injected intramuscularly followed by weekly, or bi-weekly, injections increasing in quantity 2,5,8,12,15,20 or at times up to 25 minims depending on the patient's reaction. A good flush should be obtained on each occasion with a normal patient.

It is better if the patient can have a good meal within an hour before the injection and it is a good plan to have some adrenaline available, but this is rarely necessary.

Description of the use of nicotinic acid tablets which may be handed to the patient.

METHOD OF TREATMENT PRESCRIBED.

To derive the maximum benefit from the treatment prescribed, the tablets should be taken on an empty stomach, the best time being half-an-hour before the first meal. The tablets should be well crushed up in the mouth and swallowed with half a tumbler of warm water. It is important that a good flushing of the face be obtained and at times it may be necessary to take four or five tablets in one dose to produce this re-action. The dose should be increased from one tablet each morning until it is discovered how many tablets are required to obtain a satisfactory flush and this dosage should then be continued daily.

with 5 minims, and advancing the dose slowly up to 20 minims, according to the patient's response as measured by the flushing and feeling of heat.

Most patients respond equally well to either histamine by injection ~~or~~ nicotinic acid or Ronicol by mouth. Oral treatment should be given early in the morning on an empty stomach with half a tumbler of warm water to give rapid absorption and the tablets should be chewed up well before swallowing. As individual response is marked each patient should commence with one tablet and increase the dosage slowly until a good response (flushing) is obtained. These instructions appear to be so important and so seldom understood or carried out if explained to patients, that a form as shown on the opposite page is used. Hilger (1950) and Fowler (1953) found considerable improvement from the use of procaine intravenously in their patients. A conservative dose is 4 mgm. per kilo of body weight (0.1-0.2% solutions in saline, 1 litre).

Streptomycin. It has been known from an early stage in the

trials of streptomycin that damage to the labyrinth is not infrequent after large doses of the drug. Barr (1949) has shown that a daily dose of less than 1 gram and a total dose of less than 60 grams carry a relatively small risk of vestibular damage provided there is no impairment of renal function. Where, however, the kidneys are damaged or, in cases with normal renal function, if the dose of streptomycin exceeds the above limits, the amount of the drug in the blood may rise to a concentration sufficient to damage the vestibular system. Thus these authors ~~have~~ observed evidence of vestibular disturbances in 16 out of 26 cases receiving more than 60 grams. The evidence that streptomycin may affect the hearing is less conclusive, though there is little doubt that even without a combination with dihydro streptomycin damage to the hearing may occur. The site of the damage to the vestibular system is still in dispute. Glorig and Fowler (1947) considered from their clinical studies that streptomycin injures the vestibular nerve peripherally. Winston (1948) and Dix, Hallpike and Harrison (1949) considered the lesion to be central.

Floberg (1949) using cytological methods, demonstrated on experimental animals that the localisation of such injuries is both peripheral and central.

It is not often that an undesirable effect of a drug can be turned to good account, but Fowler (1948) and others (Hamberger, 1949, Ruedi, Cawthorne, 1954) have used streptomycin as a specific neurotoxin to damage the vestibular organ in cases of vertigo unsuitable for other forms of treatment. The effect on the vestibular system is checked by daily caloric tests and Schuknecht (1957) states that the responses of the more seriously affected labyrinth will disappear first of all and that the treatment should be withdrawn as soon as this is observed. He and Hamberger (1949) have treated unilateral Ménière's disease by this method. Fowler claimed that the attacks of vertigo were completely or almost stopped for at least five to nine months. The effect on locomotion varied with the previous functional efficiency of the vestibule and the age of the subject. If the disease had caused slight damage to the labyrinth the immediate

result of streptomycin administration was severe vertigo such as is seen after surgical ablation of the labyrinth in this type of case. The older the patient the less perfect was the compensation which ultimately took place. Compensation was, however, never complete and all patients subsequently found difficulty in walking in the dark. Thus Fowler limited treatment to those patients under the age of 50 years with Ménière's disease affecting both labyrinths in whom medical treatment has failed. Personal experience of this method has been less satisfactory than Fowler's. Observation must be continued after the end of treatment since further vestibular disturbance may occur long afterwards. Intractable ataxia, though not occurring in the present series has occurred after treatment of tuberculosis with streptomycin and care must be taken to avoid this ataxia which is more disabling than Ménière's disease. In some cases the vestibular function has returned (Jongkees, 1950). In many cases it is difficult to decide from caloric tests when treatment should cease. The hearing loss in these bilateral cases may be of more

importance to the patients than the attacks of vertigo and streptomycin cannot, of course, affect this. Schuknecht (1957) has also attempted the selective unilateral destruction of the vestibular end-organs, sparing the cochlear function, by intratympanic injection of streptomycin.

Salt and fluid restriction. This method of treatment has been discussed in detail in a previous section of this paper.

Surgery. The final state in Ménière's disease, not very often reached, is total destruction of the end-organs of balance and hearing. Central compensation occurs after destruction of the vestibular end-organs and the ability to balance is in most cases thus restored. For the most part the surgical treatment of Ménière's disease has been aimed at destruction of the entire inner ear and is thus usually reserved for cases in which little or no useful hearing remains. The most reliable method of accomplishing it is by labyrinthotomy. The method advocated by Cawthorne (1943) is to open the lateral semi-circular canal and remove the membranous canal. Removal alone in our experience has not always

been sufficient to destroy the labyrinth completely and alcohol (90%) is now always injected into the vestibule at the same time. Continued labyrinthine function after removal of the lateral semi-circular canal from guinea pigs was described by Kristensen (1952) and by Lindsay (1949) in the human. No complications from this alcoholic injection such as facial palsy have been seen. Recently the operation of transtympanic destruction of the labyrinth (Lempert 1948, Schuknecht 1957) has been used in many clinics. The operation is simpler, less troublesome for the patient and is less likely to produce complications. In the present series of 429 cases of Ménière's disease it was considered that 52 (14%) required destruction of the labyrinth.

There are a number of cases of Ménière's disease in which conservative treatment has failed, but in which it is not desirable to destroy the hearing in one ear.

(1) In Unilateral Disease:

- (a) In those cases with good hearing in the affected ear.
- (b) In those cases with the hearing on the opposite side reduced by some other cause.

(2) In Bilateral Disease:

- (a) In which, as is so often found (Day, 1950; Cawthorne and Hewlett, 1954), both ears are affected early in the disease.
- (b) Less commonly, in which one labyrinth has been destroyed before the disease appears in the second ear.
- (c) In which the hearing is already poor in one ear and is found to be falling off rapidly on the opposite side. Here, if it can be achieved, halting of the loss of hearing may well be more important than the relief of the vertigo, though it is likely that the two will go hand in hand.

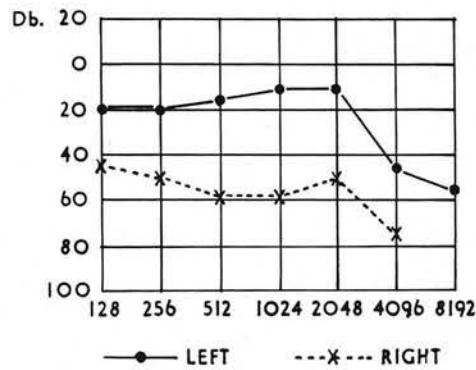
In all these cases some form of surgical treatment other than destructive surgery should be considered.

Several operations for the treatment of Meniere's disease may be considered conservative:

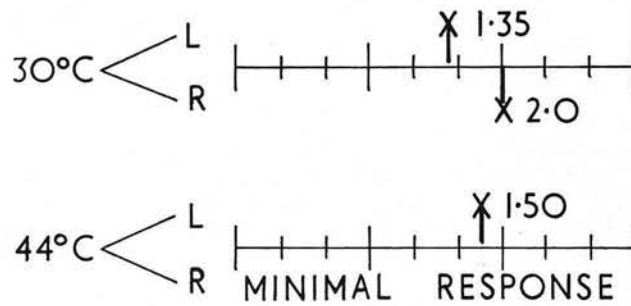
Portmann's operation (1927) of drainage of the endolymphatic sac appears in some cases to be very effective, but may be followed by a rapid fall in the hearing on the same side. It is

an operation whose value may be greatest in patients with unilateral Ménière's disease of some standing in whom the hearing on the affected side has fallen beyond church level (i.e. 30 decibels). Flett (1954) states that the operation offers a 25 per cent. chance of retaining the hearing and relieving the vertigo and tinnitus, a 61 per cent. chance of relieving the vertigo, but with a gradual loss of hearing, and that the operation fails in 14 per cent. If, of course, the alternative is destructive surgery it is often worth while trying Portmann's operation as a preliminary to destruction of the labyrinth as some of the cases will avoid the latter operation. Support has also been given by Woodman and Adams (1939) but the opinion of most authorities is that though the immediate results may be good, later changes occur, probably in the form of fibrosis around the saccus and the patient returns to his previous state, or a gradual loss of function results, rendering the operation pointless. McNally (1926) showed that following incision, cauterisation, or the application of pressure to one saccus, the

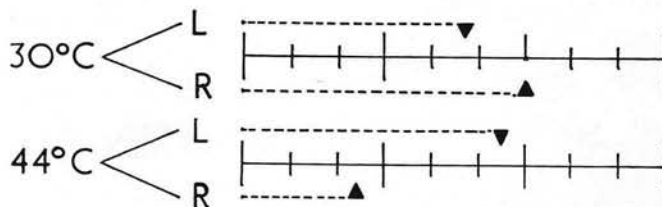
PATIENT A.T. 28-5-49



36



37



rabbit shows little disturbance of its vestibular mechanism.

The following case is an interesting illustration of the use of Portmann's operation.

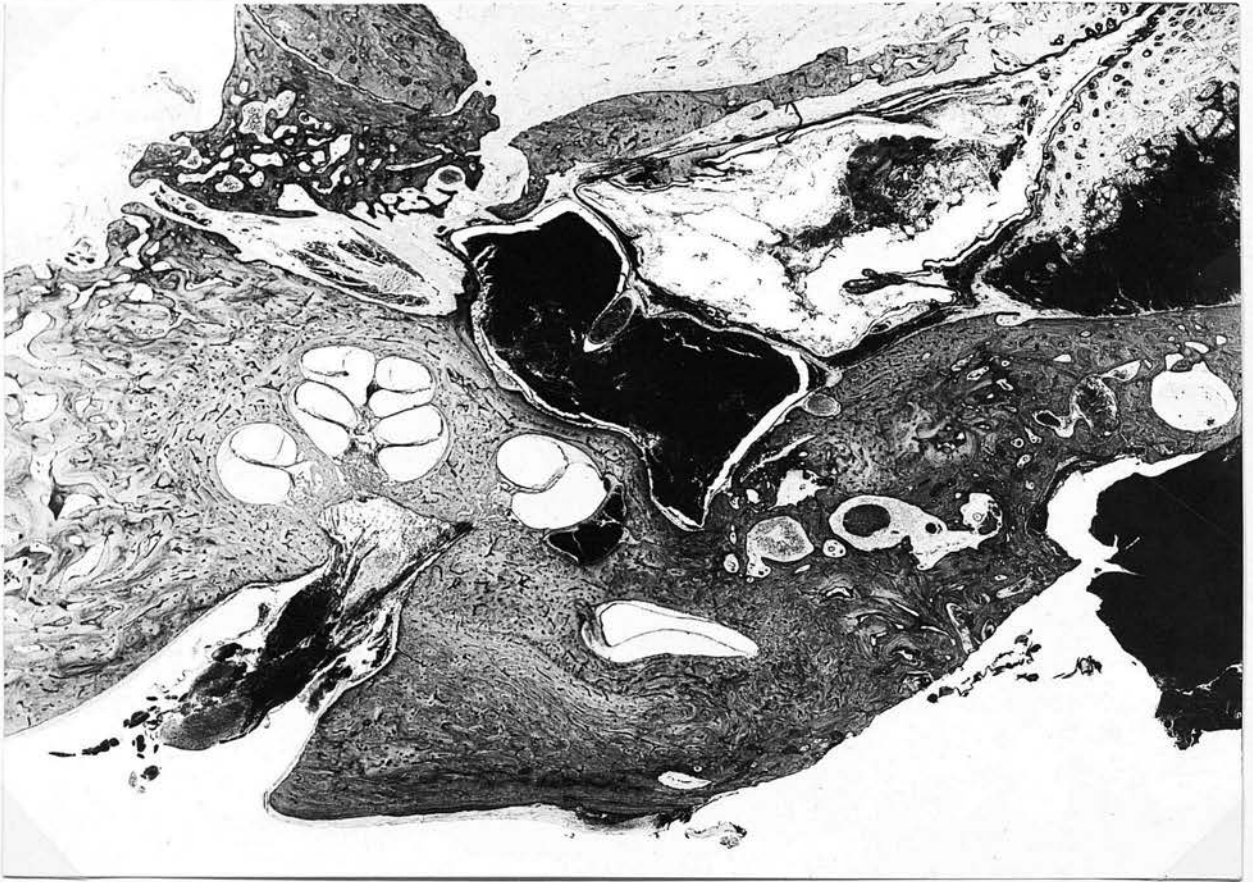
The subject, a woman of 50 years, was first seen in April 1948. She then gave a history of one month's duration of attacks of rotational vertigo preceded for some months by increasing deafness of the right ear accompanied, since the onset of vertigo, by a continuous humming tinnitus in the right ear.

Examination of the ears, nose and throat revealed nothing abnormal. Roentgenological examination of the paranasal sinuses showed mucosal thickening within the right antrum, which was washed out with negative results.

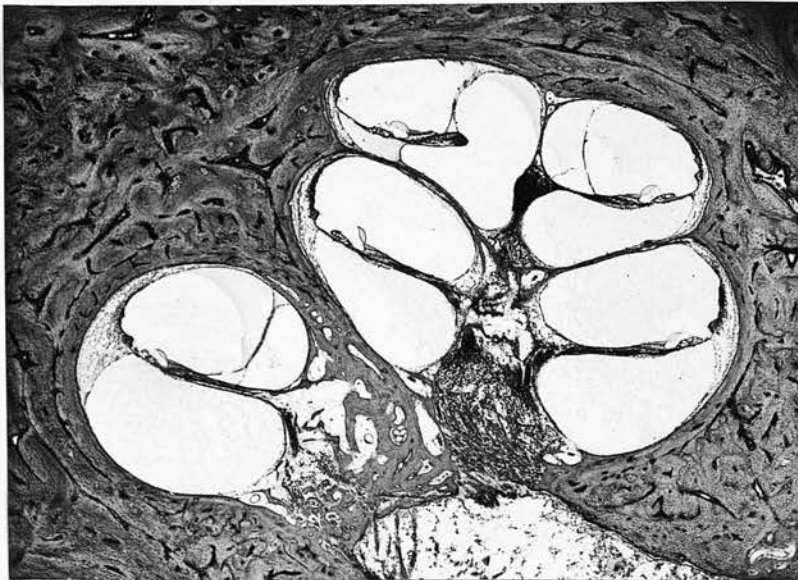
Pure-tone audiometry carried out in May 1949 gave the result shown in Figure 36. Tuning-fork tests showed the deafness of the right ear to be of the perceptive type, the Weber test being referred to the left, with a false negative Rinne test on the right mastoid. There was no spontaneous or positional nystagmus and the caloric tests gave the results shown in Figure 37. It

will be seen that there was a well-marked abnormality in the pattern of the responses, indicative of a lesion of the right labyrinth. During the next two years the vertigo continued to be very troublesome and resisted the usual forms of medical treatment, including histamine injections.

On January 3rd 1950, Portmann's operation was performed upon the right labyrinth, under nitrous oxide and oxygen anaesthesia. The bone between the lateral sinus and the posterior semi-circular canal was removed and the dura elevated. After the separation of the dura from the fossette of the saccus endolymphaticus, an escape of clear fluid was observed at this point. Whether or not the fluid was cerebrospinal fluid escaping from a small dural tear or endolymph escaping from the divided saccus, it was impossible to say. The blood pressure was lowered during the operation, and a short period of cyanosis occurred half way through the procedure. After the operation the patient remained in coma and died three days later. The pupils remained small, with a left extensor plantar reflex. At necropsy no abnormalities



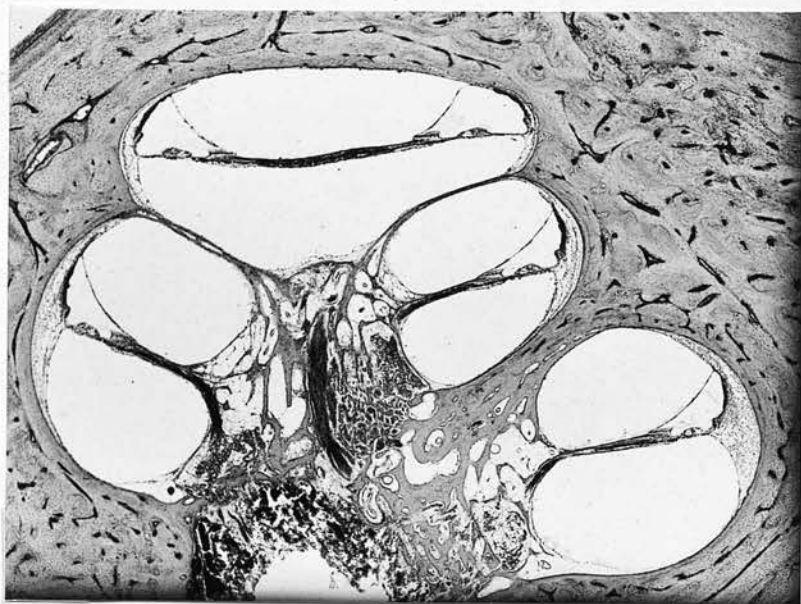
38



39

discernible by the naked eye were found in the central nervous system. The temporal bones were removed one hour after death, fixed in formalin and examined histologically at the Otological Research Unit, Queen Square.

In Figure 38 is shown a low-power photomicrograph of a horizontal section of the affected temporal bone. The middle-ear cleft is filled with a blood clot. The cochlea shows a distension of the endolymph system of a type characteristic of Ménière's disease. Posteriorly in the operation area the dura has been stripped from the posterior surface of the petrous bone. The posterior canal and the intra-petrous portion of the saccus are also shown. The saccus has been divided at the front where it passes from the bone backward into the dura by the separation of the dura onto the anterior lip of the fossette. This can be clearly seen. The section therefore shows that this critical step of the operation was successfully carried out. In Figure³⁹ is shown the cochlea at a higher magnification. As usual, the spiral ganglion and cochlear nerve fibres appear normal and no



obvious changes can be seen in Corti's organ. In figure 40¹ is shown the cochlea of the unaffected side. It is completely normal.

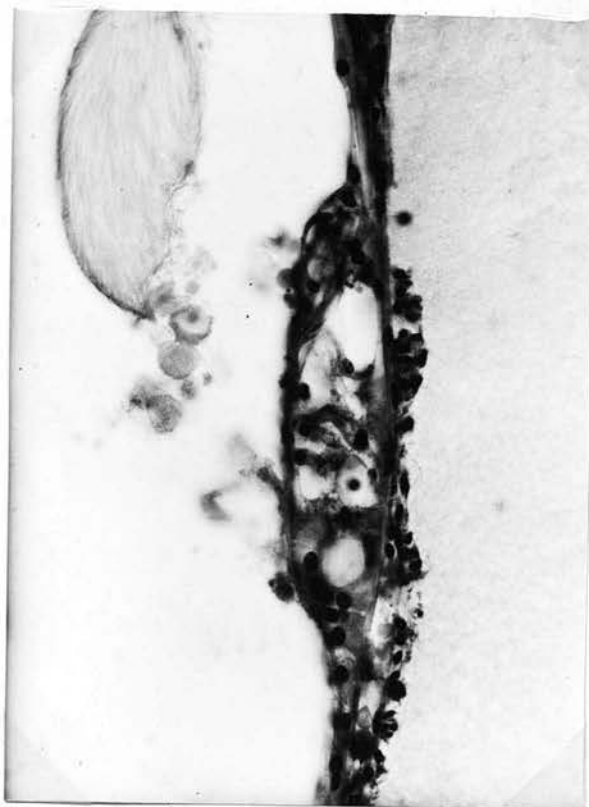
Two points of particular interest arise. They concern the histological condition of the hair cells of Corti's organ and the position of Reissner's membrane in the affected cochlea.

Corti's organ. There now seems to be an increasing measure of agreement that the hearing defect in Ménière's disease, with its peculiar characteristics including loudness recruitment, is attributable to pathological changes in Corti's organ. One of the difficulties here has been the fact that it has not been possible in any of the temporal bones which have so far been examined to demonstrate definite changes in the hair cells. In the present case, however, well-marked changes in these cells have been demonstrated. These are shown in figure 41 which comprises a number of high-power photomicrographs of the organ of Corti, taken from the anterior apical and the anterior middle turns of the two cochleae. The normal cochlea is shown on the left and the affected cochlea on the right. In spite of the fact that fixation

17



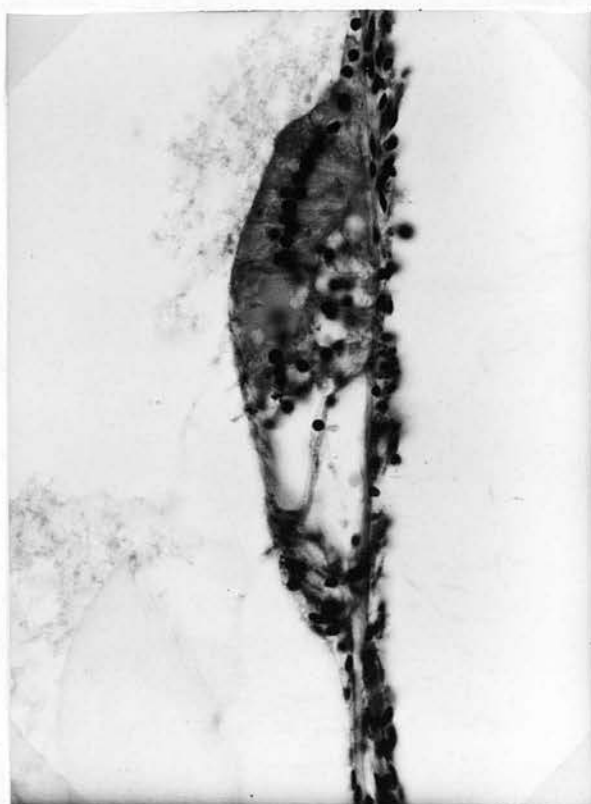
17



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17

is by formalin only, with a good deal of inevitable postmortem artefact, the difference between the two sides is not difficult to recognize. In the unaffected cochlea, the size and shape of the organ are normal, with fairly good preservation of the outer hair-cell complex. In the middle turn, in particular, the nuclei of the hair cells can be clearly seen. In the affected cochlea, however, Corti's organ is obviously shrunken, with disorganisation of the outer hair-cell complex.

Position of Reissner's membrane. This point is of particular interest in view of the possible effects of Portmann's operation. Thus, if it be assumed that the effect of the operation is to reduce the endolymph tension by permitting an escape of endolymph from the divided saccus, there might be expected some tendency of Reissner's membrane to revert to its normal position. As shown in figure 39¹ no such change seems to have occurred. The absence of any such tendency is note-worthy but cannot be taken to invalidate the theoretical basis of the operation. It is likely, for instance, that after a long-standing stretching of Reissner's



Fig. 42. A further section of the temporal bone near to Fig. 38.

membrane, growth of the membrane would occur and enable it to occupy its new position without tension.

In other words, the bulging of Reissner's membrane, so clearly seen in figure 39 cannot be taken to mean a raised endolymph pressure at the time of the patient's death. It means only that in the past there was a raised pressure forcing the membrane into its new position.

Thus Portmann's operation, carried out in a case of established Ménière's disease, would not of necessity cause any change in the position of Reissner's membrane. Nevertheless, should any further increase of endolymph volume occur, then, instead of causing a further displacement of Reissner's membrane, it would be discharged through the open saccus with minimal pressure changes in the labyrinth and, so, the purpose of Portmann's operation would be fulfilled.

Altmann (1951) has suggested a modification of Portmann's operation to make the drainage of the endolymph more permanent. An opening is made in the membranous lateral canal at the vertex



Fig. 43. High power (x260) view of saccus.

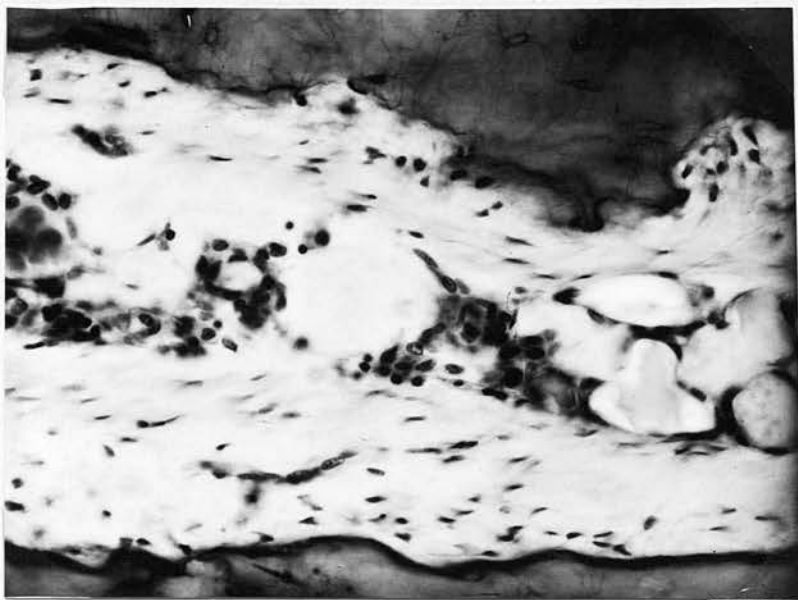


Fig. 44. Higher power (x16) view of saccus.

of its convexity to drain the endolymph into the perilymphatic space. It is now well recognized that tearing of the membranous canal during fenestration does not always destroy the labyrinth, but it is an interesting observation that the labyrinth in a case of hydrops of the endolymph appears to be more easily destroyed than is the more healthy labyrinth in patients with otosclerosis or with vertigo after mastoidectomy. Certainly in our hands this operation has been followed rapidly, if not at once, by loss of labyrinthine function.

Decompression of the perilymph (Femenić, 1955) has not been proved of value in the treatment of Ménière's disease.

Plugging of the horizontal canal (Altmann, 1951) may in certain cases relieve the dizziness for a time, but the hearing often is also depressed and sometimes completely lost. The effect on the vertigo bears little relation to the site of the lesion whether in the canal or in the utricle.

Day's (1949) method of diathermy coagulation of the vestibular end organs is by no means certain of completely destroying the

function of the organ of balance or of retaining useful hearing. The animal experiments of both Proctor (Lindsay, 1949) and Schlander (1949) have shown that intravestibular instrumentation usually results in extensive fibrosis and degeneration of the sensory organs.

Ultrasonic methods of treatment of Ménière's disease have not been fully investigated in this country. Arslan (1953) uses an ultrasonic beam to destroy the endorgans of balance only, Barbe (1956) describes a method of relieving the symptoms of Ménière's disease by ultrasonotherapy without destroying the labyrinth. The initial success of certain of Day's operations and the histological evidence obtained from monkey experiments (Day and Lindsay, 1949) encourage the search for a means of interrupting vestibular function without injuring hearing. On the other hand, Day now feels that it is likely that the cochlea is primarily affected in Ménière's disease, certainly it is likely that cochlear symptoms in many cases will persist after operation or become still more troublesome to the patient, so

that other lines of investigation should be explored.

The inner ear derives no nerve supply from the tympanic plexus, so that it is unlikely that operations on the plexus will affect lesions of the labyrinth.

The anatomical basis of Rosen's (1951) division of the chorda tympani is not established and we have no personal experience of the operation.

It is interesting that Escat in 1906 (Portmann, 1929) suggested that Ménière's disease might be related to vascular spasm. In 1928 Terracol stated that the autonomic nervous system had a notable influence on inner-ear function and Portmann (1929) showed that vasodilatation produced hypo-excitability of the labyrinth. For several years lesions of the inner ear have been mentioned among the indications for sympathectomy (Murphy, 1933; Biancalana, 1939; Passe, 1949 and 1951).

Injectations into the stellate ganglion have been used in many clinics for the treatment of hydrops of the labyrinth

(Hibler, 1948; Schubert, 1949; Passe, 1951), but it appears effective only in some early cases of this condition, most of which would have responded equally well to adequate medical treatment. In the same way, tinnitus and deafness occurring together or apart are little influenced unless the lesion is very recent. Unfortunately, complications from the injection into the region of the stellate ganglion by which ever route is chosen are unpleasant, at times serious and by no means rare. Also the results of stellate injection seem seldom to give any really helpful lead in the selection of cases for sympathectomy. For these reasons, after the trial of the method in some 50 patients in some of whom the injection has been repeated up to twelve times and after consideration of the experience of others, we have found ourselves using the stellate injection less and less.

Cervico-dorsal sympathectomy has been used in the treatment of 29 cases of Ménière's disease by Cawthorne and Lewis (King's series) and in 19 cases by myself. In spite of the possibilities, complications have not been common in this series and lasting

Table I.

Time Since Operation

to 1yr. to 2yrs. to 3yrs. to 4yrs. to 5yrs. >5yrs.

King's
29 cases

2

8

1

4

6

8

M.S.H.
14 cases
to Feb. '56.All 4 to 5 yrs. (average $4\frac{3}{4}$ yrs.) except 2 bilateral cases, one of which is still improved 18 months after operation.5 cases
since
March '56.

Table II.

Vertigo.

King's

M.S.H.

Total
CasesTotal
Cases

Bilateral Cases Vertigo ceased or much improved

5

Vertigo improved

4

10

1

10

Unilateral Cases Vertigo ceased or much improved

9

3

Vertigo improved

4

18

1

9

17

28

10

19

serious effects have not been encountered.

The time since operation is shown in Table 1. The King's series are spread over the past six years. Twelve of my own cases were operated on approximately five years ago and their progress has been carefully watched since that time.

Table II shows the effect of the operation on the vertigo in the two series. Several of the bilateral cases have been of long standing with severe vertigo and almost total deafness and these, unfortunately, have not received much benefit. Unilateral cases on the whole do better than bilateral ones, probably because the disease is usually more severe when both ears are affected. It is interesting that improvement or disappearance of the vertigo may not occur in some cases for up to a month after the operation. In several cases the vertigo diminished in frequency and severity for several months and then gradually relapsed to its former state. These have been classified as unchanged, in spite of the temporary improvement.

It has been difficult to assess the results of the operation

upon hearing because this symptom varies so much in the natural course of the disease. The opinion of the patient, the pure tone audiogram and the speech audiogram often did not coincide. On the whole the audiometric changes were slight, an improvement of more than 5 to 10 decibels in the speech range being seldom recorded. If fluctuation of hearing were a noticeable feature of a case, it tended to disappear after operation and the hearing became more steady. The hearing level remained within the limits of the previous fluctuation, but usually at about its upper level. Many of the unilateral cases have shown no further loss of hearing over the course of several years and it is probable that the operation is effective in preventing or slowing up progression of deafness.

In bilateral Ménière's disease it therefore seems reasonable to recommend sympathectomy in the better ear if the deafness is progressing unchecked by medical measures. The operation gives a better chance of success if it is done before much loss has occurred,

Tinnitus has been improved in 10 cases. The presence of

Table IIIOverall Assessment

		King's	M.S.H.
Much improved	} worth while benefit	8	8
Improved		10	3
			3 I.S.Q.
Worse or I.S.Q.		11	11
			5 worse
Total		29	19

Table IV.Duration of Disease before Operation.

	King's							M.S.H.						
Years	1	-2	-3	-4	-5	>5	Total	1	-2	-3	-4	-5	>5	Total
No. of cases	5	6	4	4	2	8	29	-	3	3	4	3	6	19
Vertigo improved	3	3	3	2	2	4	17	-	2	3	1	2	2	10
Hearing improved	1	0	1	2	1	0	5	-	2	2	1	1	-	6
Hearing unchanged (static)								-	2	3	1	1	-	7
Hearing worse								-	-	1	1	2	2	6

intolerance or distortion of sound was recorded in 20 cases, in 7 of whom there has been an improvement. The operation has produced no appreciable change in the caloric test pattern in either series.

Table III shows the overall assessment of the cases taking all symptoms into consideration.

We have not as yet been able to decide before operation which cases will improve and which will not. The largest proportion of the cases have been in the later age groups and of over three years' duration (Tables IV and V). (Harrison 1956). It appears that the operation is most likely to succeed in the young or middle aged with a hearing loss of not more than 40 decibels, and that the duration of the vertigo is of less importance in the prognosis than the severity of the condition; the more severe the symptoms the less likely is sympathectomy to be successful. Sympathectomy in other parts of the body is less satisfactory in long standing and elderly cases, and the operation is inadvisable in Ménière's disease over the age of fifty-five.

Table V.Ages

Ages (yrs)	King's					M.S.H.				
	0-30	-40	-50	>50	Total	0-30	-40	-50	>50	Total
No. of cases	3	10	8	8	29	1	4	7	7	19
Vertigo improved	3	6	5	3	17	-	2	4	4	10
Hearing improved	2	1	1	1	5	-	3	2	1	6
Hearing unchanged (static)						1	1	3	2	7

Unfortunately it is not always easy to diagnose the very early case of Ménière's disease and medical treatment, which should always be given a trial, is often long drawn out, so that operation is seldom called for in a really early case.

Intracranial section of the vestibular part only of the eighth nerve was first described by McKenzie (1932) and later by Dandy (1937), it is an intracranial operation in the region of the cerebello-pontine angle and is thus a major procedure, not without risk. As with other methods it aims at the interruption of impulses arising in the labyrinth and passing to the brain. Theoretically this appears an excellent approach to the problem; but the disease may cause such distortion of hearing on the affected side that any but the softest tones are distressing. Thus patients often prefer to be without the remainder of the hearing on the affected side as they are unable to listen to loud sounds such as the wireless without discomfort. In many cases the attacks continue without the vertigo, and deafness and tinnitus increase so that soon the hearing becomes valueless even

if it were not so beforehand.

In certain cases it is claimed that hearing is improved after this operation, Crowe (1938) and Dandy (1941) states that tinnitus is cured in half the patients after operation, but he admits that post-operative visual disturbances which are severe and permanent in bilateral cases, occur when the patient is in motion. Jumbling of objects is noticed and the patient is unable to focus the eyes sharply and tends to stagger in the dark. Cawthorne (1956) states the operation should be reserved for unilateral cases with good hearing on the affected side, and for bilateral cases where one side only is active and where the hearing is still useful.

The ability to re-orientate himself after operation varies with the type of patient and the severity of the reaction. Considerable help may be had from exercises which encourage the patient to move the head and eyes freely in all directions. If these commence gradually their scope may be extended so that the patient can with confidence execute movements that produce giddiness and thus is slowly able to overcome this symptom. In

a co-operative patient daily exercises, preferably in a class, for ten days may be sufficient, but in slower cases a month may be required, (Cawthorne, 1943).

No certain means of controlling tinnitus is as yet available. Heavy sedation may be necessary, and in extreme cases prefrontal leucotomy may have to be considered.

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